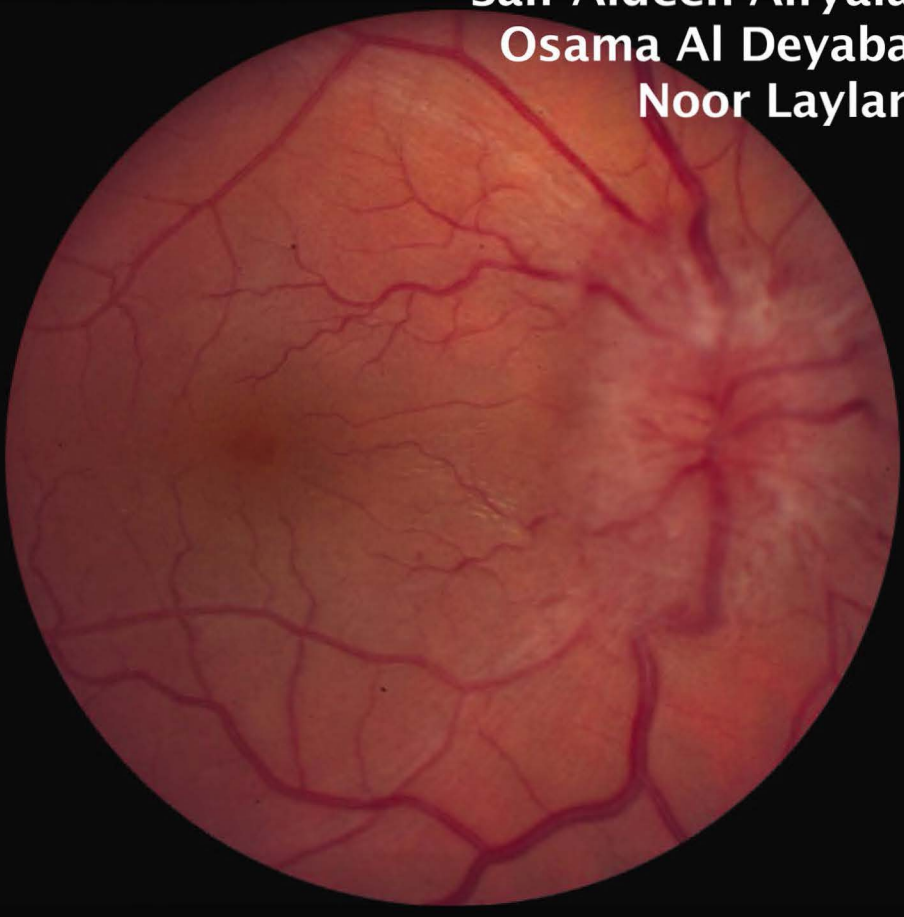
Emergencies in Neuro-Ophthalmology

A Case Based Approach

Second Edition

Andrew G Lee
Saif Aldeen Alryalat
Osama Al Deyabat
Noor Laylani



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NEW JERSEY · LONDON · SINGAPORE · BEIJING · SHANGHAI · HONG KONG · TAIPEI · CHENNAI · TOKYO

Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

EMERGENCIES IN NEURO-OPHTHALMOLOGY
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ISBN 978-981-12-9216-3 (hardcover)
ISBN 978-981-12-9217-0 (ebook for institutions)
ISBN 978-981-12-9218-7 (ebook for individuals)

For any available supplementary material, please visit
https://www.worldscientific.com/worldscibooks/10.1142/13813#t=suppl

Printed in Singapore

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Preface

The management of emergent neuro-ophthalmic conditions can be a life saving encounter for the general ophthalmologist. This book is designed to help comprehensive ophthalmologists make emergency triage decisions for initial evaluation and treatment of potentially vision- or life-threatening conditions. This text is case-based and is intended to provide the reader with the opinions and expertise of two neuro-ophthalmologists: Dr. Lee, an ophthalmology-based neuro-ophthalmologist, and the other, Dr. Brazis, a neurology-based neuro-ophthalmologist. Dr. Moghul and Dr. Policeni collected and collated the case vignettes during their fellowship with Dr. Lee at the University of Iowa Hospitals and Clinics.

It is the goal of this text to provide a concise, easy to read, and practical guide to the emergent evaluation of these neuro-ophthalmic conditions. This book is designed to be a quick read and not to be all-inclusive or comprehensive. The reader is directed to longer and more comprehensive neuro-ophthalmic texts for this information. It is also not our intention to provide anatomy, pharmacology, physiology, or other basic mechanisms of disease. Instead, this text is meant to be a quick reference and resource for the clinician in the Emergency Room or in the clinic facing a potentially vision- or life-threatening emergency, and to provide immediate guidance for potentially "high stakes" decision-making. We also wish to emphasize that the recommendations of this text represent the authors' own opinions on management and are not intended

to be, nor should they be, construed as a "standard of care." The case vignettes are based upon real clinical cases, but the clinical details of each case have been modified for teaching purposes and represent composite rather than individual histories.

Each case vignette is composed of the relevant and concise medical history, the neuro-ophthalmic exam findings, the clinical and exam findings with demonstrative figures, and, finally, the expert opinion for management provided by Dr. Lee and Dr. Brazis.

We hope that the reader will enjoy the format and content of this text and we invite comments and feedback on the utility of our work.

Andrew G. Lee, MD,
Saif Aldeen Alryalat, MD,
Osama Al Deyabat, MD,
Noor Laylani, MD

Acknowledgments

The authors would like to thank authors of previous versions, Dr. Paul W. Brazis, Dr. Mansoor Mughal, and Dr. Fabiana Policen.

Dr. Lee would like to recognize and thank his patient and always loving wife, Hilary A. Beaver, MD, for putting up with the writing and now revision of yet another textbook in medicine (book #15). As the saying goes, "No man succeeds without a good woman behind him," and in my case, I have had the honor of having five supportive women in my life: my wife (Hilary), my mother (Rosalind Lee, MD), my two daughters (Rachael and Virginia), and my sister (Amy Lee Wirts, MD), so I feel blessed times five. I also thank my father (Alberto C. Lee, MD) for instilling in me a passion for medicine and my brother (Richard Lee) for being a source of real world wisdom and providing a reality check from the non-MD side of the family. Finally, I thank Dr. Brazis, my Emeritus co-editor, for being the best friend and neuro-ophthalmology buddy a guy could ask for.

Contents

About the Authors		v
Preface		vii
Acknowledgments		ix
Chapter 1A	Acute Painful Ptosis, Complete Ophthalmoplegia with a Red Eye	1
Chapter 1B	Chronic Painless Ptosis, Complete Ophthalmoplegia with a Red Eye	9
Chapter 2A	Acute Painless Homonymous Hemianopsia	15
Chapter 2B	Acute Painful Homonymous Hemianopsia	21
Chapter 3A	Acute Bilateral Optic Disc Edema	25
Chapter 3B	Subacute Bilateral Optic Disc Edema	33
Chapter 4	Acute Homonymous Hemianopsia in Febrile Patient	41
Chapter 5	Acute Painless Isolated Sixth Nerve Palsy	49
Chapter 6	Acute Progressive Bilateral Ophthalmoplegia with Mental Status Change	57
Chapter 7	Acute Unilateral Optic Neuropathy	63
Chapter 8A	Acute Pupil Spared Third Nerve Palsy	75
Chapter 8B	Acute Pupil Involved Third Nerve Palsy	85

Chapter 9	Acute Proptosis with Red Eyes	91
Chapter 10	Acute Visual Loss in a Leukemia Patient	103
Chapter 11	Acute Ophthalmoplegia After Vomiting	109
Chapter 12	Acute Anisocoria	115
Chapter 13	Optic Disc Edema with a Macular Star Figure	121
Chapter 14	Acute Transient Monocular Visual Loss	127
Chapter 15	Jaw Pain and Headache in an Elderly Woman	137
Chapter 16	Acute Bitemporal Hemianopsia	141
Chapter 17	Acute Anisocoria with Neck Pain	147
Chapter 18	Acute Painful Ophthalmoplegia	155

Index 161

CHAPTER · 1A

Acute Painful Ptosis, Complete Ophthalmoplegia with a Red Eye

CASE NO. 1A

A 55-year-old white female presented in the Emergency Room (ER) with a chief complaint of the onset of a headache during the previous four days. The headache resolved the following day, but she began having swelling of her right eye (OD). This worsened over the following few days and she developed diplopia. She related no eye pain but did complain that the right side of her face was numb.

On examination, her visual acuity was 20/100 OD and 20/20 OS. The pupillary examination showed a dilated and fixed pupil OD; the pupil OS was normally reactive to light. Ocular motility showed complete ophthalmoplegia OD and was full OS (Fig. 1A.1). External examination showed complete ptosis and marked proptosis OD (Fig. 1A.2). Hertel measurement showed 7 mm of proptosis OD. There was a prominent orbital bruit over the right eye. Slit lamp examination showed dilatation of the conjunctiva and episcleral vessels with diffuse injection. There was no chemosis. The cornea was clear, the anterior chamber was quiet, and the lens was normal. Examination OS was unremarkable. Intraocular pressure was 26 mm Hg OD and 18 mm Hg OS. Ophthalmoscopic examination was normal in each eye.

Fig. 1A.1. Ocular motility photography showing the almost complete ophthalmoplegia in the right eye.

Fig. 1A.2. External photography showing the complete right ptosis.

Discussion

Dr. Brazis' comments: The above clinical scenario is most consistent with a carotid-cavernous sinus fistula (CCF), which is an abnormal communication between the cavernous sinus and the carotid arterial system. CCFs can be classified by etiology (e.g. traumatic versus spontaneous), by velocity of blood flow (e.g. high versus low flow), or by anatomy (e.g. direct versus dural; internal carotid artery versus external carotid artery supply versus both). In this patient, I would be concerned about a direct high flow connection between the cavernous segment of the internal carotid artery and the cavernous sinus. These

fistulas are of a high flow type, and because they are often caused by a single tear in the arterial wall, they are thus called direct CCFs.

Direct CCFs represent 70% to 90% of all CCFs in most large clinical series. They occur in both men and women and may occur at any age. A direct CCF results from a single tear in the wall of the cavernous segment of the internal carotid artery. This produces a direct connection between the artery and one or more of the venous channels within the cavernous sinus. Direct CCFs most often are the result of head trauma, especially motor vehicle accidents, fights, and falls. The injury may be extremely severe or quite trivial. A substantial minority of direct CCFs are caused by the rupture of a pre-existing aneurysm of the cavernous segment of the internal carotid artery. Direct CCFs may also be iatrogenic, occurring after various diagnostic and therapeutic procedures (e.g. carotid endarterectomy, cranial and percutaneous retro-Gasserian procedure for the trigeminal neuralgia, transphenoidal surgery, or maxillofacial surgeries).

Although direct CCFs are usually not thought to be life threatening, there are numerous reports of patients experiencing significant and even fatal epistaxis, subarachnoid hemorrhage, or intracerebral hemorrhage from a rupture of the fistula. The ocular manifestations of a direct CCF are usually ipsilateral to the side of the fistula but may be bilateral or even contralateral. The lateralization of ocular manifestations depends on the venous drainage of the cavernous sinuses, including the connections between the two sinuses through the intercavernous sinuses and the basilar sinus, the presence or absence of cortical venous drainage, and the presence or absence of thrombosis within the sinus or a superior ophthalmic vein on one or both sides.

Proptosis is a common sign, occurring in almost all patients. In most cases, proptosis develops rapidly on the side of the fistula and becomes pronounced within a few days. In the early stages of a direct CCF, the eyelids may become moderately or severely swollen. When the superior ophthalmic vein is enlarged, the medial portion of the upper eyelid may be ptotic or swollen. Conjunctival chemosis, to some degree, occurs in most patients. In more severe cases, the inferior palpebral conjunctiva may prolapse through the interpalpebral fissure

and rarely may cause conjunctival necrosis or superinfection. As arterial blood is forced anteriorly into the orbital veins, the conjunctival and episcleral veins becomes dilated, tortuous, and filled with arterial blood. This "arterialization" of the conjunctival vessels is the hallmark of a CCF. Although it may initially be mistaken for conjunctivitis or episcleritis, the dilation and tortuosity of the affected vessels is usually quite distinctive, running to the limbus and often arching back in a loop. Ocular pulsations are caused by transmission of the pulse waves from the internal carotid or ophthalmic artery to the ophthalmic veins. Abnormal ocular pulsations may be visible on applanation or other tonometry and may sometimes produce pulsating exophthalmos that may be palpalble.

Exposure keratopathy is the most frequent corneal sign encountered in patients with a direct CCF. The keratopathy may be aggravated by a concomitant trigeminal neuropathy caused by injury or by the effects of the fistula on the trigeminal nerve within the cavernous sinus. In some patients with a direct CCF, the initial symptom may be a pulsatile tinnitus or subjective bruit, which may or may not be associated with an audible bruit. Diplopia occurs in 60% to 70% of patients with direct CCF. The diplopia may be caused by dysfunction of one or more of the ocular motor nerves, the extraocular muscles, or both, and the degree of motility limitation varies from mild to complete ophthalmoplegia. Visual loss associated with a direct CCF may be immediate or delayed. Immediate visual loss is usually caused by ocular or optic nerve damage at the time of the head injury. Delayed visual loss is usually caused by retinal dysfunction, but it may be related to vitreous hemorrhage, central retinal vein occlusion, angle closure glaucoma from anterior rotation of the ciliary body, anterior ischemic optic neuropathy, or even corneal ulceration. Dilation of the retinal veins may be seen and can be asymptomatic but can produce venous stasis retinopathy or even frank central retinal vein occlusion with macular edema and diffuse retinal hemorrhages.

Occasionally, patients complain of facial pain in the distribution of the first and rarely the second division of the trigeminal nerve. Some patients will have decreased corneal sensation, decreased facial sensation, or both, perhaps related to ischemia or compression of the ophthalmic or maxillary divisions of the trigeminal nerve within the cavernous sinus. Glaucoma may develop in up to

30% to 50% of patients, and most commonly, the rise in intraocular pressure is due to increased episcleral venous pressure or orbital congestion. Neovascular glaucoma may also occur associated with chronic retinal hypoxia and retinal neovascularization.

Finally, as in this patient, a direct CCF should be suspected in any patient who suddenly develops chemosis, proptosis, and a red eye. If there is no history of trauma, one should consider the possibility of a ruptured cavernous aneurysm.

Dr. Lee's comments: Dr. Brazis has provided a nice summary of direct and indirect CCFs. The indirect CCF may spontaneously involute, and in the absence of vision-threatening proptosis, exposure keratopathy, debilitating ophthalmoplegia, visual loss, or severe pain, many patients can be observed for spontaneous resolution from the natural history of thrombosis in these lesions. Non-catheter based neuroimaging (e.g. magnetic resonance imaging (MRI) and MR angiography (MRA) or computed tomography angiography (CTA)) might be sufficient to suspect the diagnosis, but most patients require catheter angiography for both diagnostic confirmation and therapeutic intervention. We have also used orbital ultrasound to follow the patient for spontaneous thrombosis and determine if clinical worsening might be paradoxically related to radiographic thrombosis and not an increase in the flow in the CCF. Halback et al. reviewed the angiographic and clinical data from 155 patients with CCF. The features associated with an increased risk of morbidity and mortality included the following:

- presence of a pseudoaneurysm
- large varix of the cavernous sinus
- venous drainage to cortical veins, and
- thrombosis of venous outflow pathways distant from the fistula.

The clinical signs and symptoms of potentially "hazardous" CCFs included:

- increased intracranial pressure
- rapidly progressive proptosis

- diminished visual acuity
- hemorrhage and
- transient ischemic attacks.

The cortical venous drainage from the carotid cavernous fistula is due to occlusion or absence of the normal venous outflow pathways and can produce increased intracranial pressure or intraparenchymal hemorrhage. Cavernous sinus varix and extension into the subarachnoid space (with an associated risk of potentially fatal subarachnoid hemorrhage) are also considered to be angiographic risk factors for morbidity and mortality. Standard catheter angiography in these patients might be diagnostic, prognostic, and, in some cases, therapeutic (i.e. angiographically induced thrombosis of the CCF). Direct CCF, on the other hand, typically require catheter angiography as the clinical signs and symptoms are more acute and severe, and as Dr. Brazis mentioned, the catheter angiogram can be diagnostic and helps to establish the direction of flow (anterograde and retrograde) and any associated cortical venous drainage. During the same, or more commonly during sequential sittings, a therapeutic angiogram can include endovascular treatment of the CCF.

CT scanning, CTA, MRI, and MRA can be used to support the diagnosis of CCF, showing an enlargement of the extraocular muscles, dilation of one or both superior ophthalmic veins, enlargement of the affected cavernous sinus, and abnormal intracranial vessels (e.g. enlarged or increased flow voids on MRA or MRI in cavernous sinus). The ultimate gold standard diagnostic test, however, is catheter angiography.

Contrast brain MRI in this patient demonstrated right proptosis, an enlarged flow void inside the right cavernous sinus, and an enlarged superior ophthalmic vein (Figs. 1A.3 and 1A.4). Catheter angiography revealed an internal carotid artery aneurysm (Fig. 1A.5) as the cause of the CCF.

The optimum treatment of a direct CCF is closure of the abnormal arteriovenous communication with preservation of the internal carotid artery patency. Endovascular closure of direct CCF is most often accompanied by embolization using a variety of agents, primarily coils and detachable balloons.

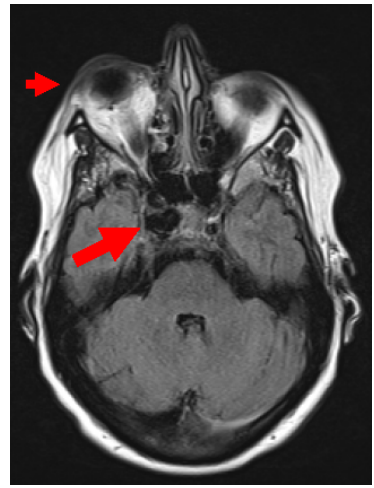

Fig. 1A.3. Brain MRI axial T1 without contrast demonstrates right proptosis (small arrow) and an enlarged flow void inside the right cavernous sinus (large arrow).

Fig. 1A.4. Brain MRI Axial T2 demonstrates the enlargement of the right superior ophthalmic vein (arrow).

Complications most often result from balloon occlusion of a direct CCF when there is planned or unplanned occlusion of the internal carotid artery. These complications, primarily those related to a reduction or interruption of the blood supply to the ipsilateral eye and cerebral hemisphere, include stroke and

Fig. 1A.5. Right carotid angiogram demonstrates an aneurysm in the internal carotid artery (arrow).

even death. Once the fistula is successfully closed, most of the ocular symptoms and signs resolve or will at least improve and do not recur. Of all the symptoms and signs of a direct CCF, visual loss is least likely to improve after successful treatment even when the internal carotid artery remains patent.

CHAPTER · 1B

Chronic Painless Ptosis, Complete Ophthalmoplegia with a Red Eye

CASE NO. 1B

A 69-year-old man presented with a 12-week history of a red eye OS, which was initially felt to be "conjunctivitis" by an outside eye doctor, and was treated with topical antibiotics for two weeks, then with topical antihistamines for two weeks, following which topical antivirals were added, and finally topical steroids without improvement. His symptoms worsened and he developed double vision, which was worse on upgaze. He also noticed a "whooshing" sound in his ears, more noticeable just before going to sleep. He denied any periocular pain, headache, or visual blurring. There was no history of trauma, as well as no history of thyroid eye disease, and he did not smoke cigarettes. The remainder of his medical history was non-contributory.

On examination, visual acuity was 20/20 OU. There was no relative afferent pupillary defect or anisocoria. There was 2 mm of ptosis in the left upper lid (Fig. 1B.1) and mild to moderate lid edema OS. Slit lamp examination showed diffuse subconjunctival hemorrhage OS with dilated and tortuous episcleral and conjunctival vessels extending to the limbus and looping back (Fig. 1B.2). The intraocular pressure (IOP) was 12 mm Hg OD and 28 mm Hg OS. Optic disc examination showed a cup-to-disc ratio of 0.3 OU, and the remainder of

Fig. 1B.1. External photograph showing a left ptosis.

Fig. 1B.2. The left eye had a –2 underaction of elevation with a 15 prism diopter left hypotropia in upgaze. The left eye showed a left diffuse subconjunctival hemorrhage, with tortuous vessels suggestive of "arterialization" of the episcleral vessels.

the fundus exam was normal. Hertel measurement showed mild proptosis OS of 2 mm. Goldmann perimetry and OCT (optical coherence tomography) were normal OU. The left eye had a –2 underaction of elevation with 15 prism diopters of left hypotropia in upgaze.

Dr. Lee. In a patient with a chronic "red eye" unresponsive to multiple different topical therapies, the general ophthalmologist should consider alternative etiologies to the typical "red eye" list. In light of this patient's additional symptoms (e.g. diplopia, ptosis, and proptosis), the clinical localization of the problem shifts from the anterior segment to the orbit. The distinctive clinical sign here is the "arterialization" of the conjunctival and episcleral vessels (Fig. 1B.2), with the classic dilated and tortuous vessels extending to and from the limbus. Interestingly, the intervening conjunctiva is often white, also giving the clinician a clue that the etiology is not a typical allergic, inflammatory, or infectious "conjunctivitis." The additional symptom of a subjective bruit in this case suggests a vascular etiology, and the next most appropriate step is imaging. Elevated IOP and secondary glaucoma can occur due to orbital congestion or increased episcleral venous pressure. Rarely, patients may have angle closure from anterior rotation of a swollen ciliary body. Treating the IOP with glaucoma drops may be useful as a temporizing measure, but the underlying etiology needs to be identified and treated. I would consider CCF to be the leading clinical diagnosis in a case like this one. The applanation tonometry mires sometimes give a clue to an increased pulse pressure in the measurement of the IOP. Orbital ultrasound might show a dilated superior ophthalmic vein, and arterialization of flow can be obtained using orbital Doppler flow studies. CT scan or MR scan typically shows the dilated superior ophthalmic vein and might show enlargement or even flow voids in the cavernous sinus. Clinical or radiographic evidence for cortical venous drainage should be sought and might be an indication for more aggressive treatment for a carotid cavernous fistula.

Discussion

Dr. Brazis. The above clinical scenario is most consistent with a CCF. The differentiating features for direct and high flow versus indirect and slow flow fistula have been discussed previously.

Course. Cranial MRI/MRA (Fig. 1B.3) showed a dilated left superior ophthalmic vein with arterialized flow. There was no clinical or radiographic evidence for cortical venous drainage. The patient was observed initially but

Fig. 1B.3. MRI shows a dilated left superior ophthalmic vein.

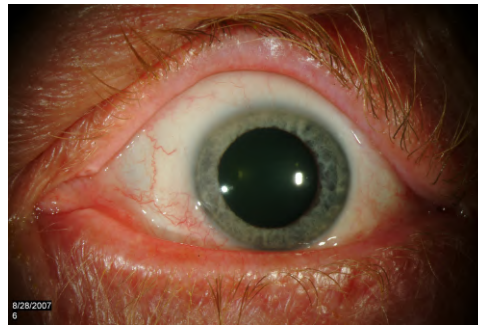

Fig. 1B.4. Color photograph of the left eye (after dilation) following successful obliteration of the CCF, and with endovascular coiling procedure shows marked resolution of the arterialization of the conjunctival and episcleral vessels.

continued to worsen and underwent a diagnostic catheter angiogram that confirmed the diagnosis of an indirect CCF with internal carotid artery feeders, and this was followed by an endovascular closure of the fistula. The subjective bruit immediately resolved after the procedure, and over the next two months, the ptosis, lid edema, proptosis, ophthalmoplegia, and red eye all completely resolved (Fig. 1B.4).

Practice Essentials

— There are two main types of carotid cavernous fistulas: direct fistula, which represents the more severe form that usually presents after trauma, leading to laceration of the cavernous segment of the internal

carotid artery, and indirect fistula, which represents the relatively benign form with a more insidious onset that mostly resolves by itself.

— Symptoms related to the fistula can be due to mass effect, including proptosis, raised intracranial, or intraocular pressure, or can be related to nerve palsy, by compressing a nerve within the cavernous sinus (i.e. third, fourth, V1 and V2 of the fifth, sixth).

— In a patient with a chronic "red eye" unresponsive to multiple different topical therapies, the general ophthalmologist should consider alternative etiologies to the typical "red eye" list.

— Imaging studies of choice are those that can capture arterial flow, including MRA and CTA, in addition to the more invasive angiography, which represent then gold standard, if other studies are negative and still in doubt.

— Mostly unilateral (search literature)

— Management includes endovascular closure of the fistula, which can result in the resolution of symptoms.

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CHAPTER · 2A

Acute Painless Homonymous Hemianopsia

CASE NO. 2A

A 67-year-old woman presented in the Emergency Room (ER) complaining of a grayish cloud over her right side vision, which started in the morning. She also related some imbalance of walking that she felt was due to her visual field defect. When the symptoms did not resolve after about an hour, she decided to seek medical attention. Past medical history was significant for hypertension and diabetes. She was on oral antihypertensive and diabetic treatments. She did not smoke or drink. She had no prior ocular history. She denied any other neurologic signs or symptoms. There was no headache, jaw claudication, or temporal artery tenderness.

On examination, the patient's visual acuity was 20/25 in each eye. External examination was unremarkable and the temporal arteries were normal. Ocular motility was full in both eyes. The Humphrey visual field (Fig. 2A.1) revealed a dense right homonymous hemianopia. Slit lamp examination was normal OU. Ophthalmoscopy was unremarkable OU.

Discussion

Dr. Brazis. A complete right homonymous hemianopia in this case indicates damage to retrochiasmal pathways on the left side. Because the homonymous

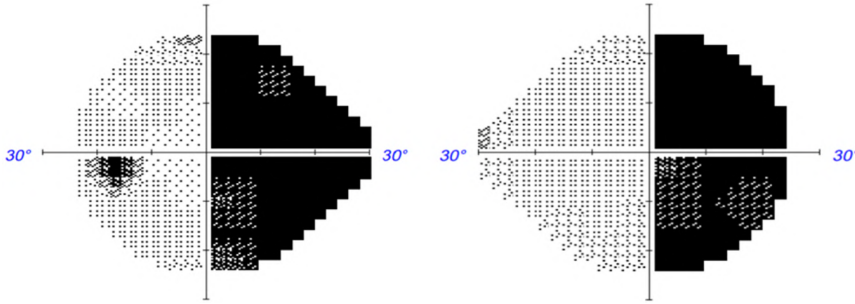

Fig. 2A.1. Humphrey visual field showing a right congruous homonymous hemianopia.

hemianopia is complete, localization to specific retrochiasmal structures (e.g. optic tract, occipital lobe, etc.) cannot be determined without neuroimaging. However, an acute homonymous hemianopia without other neurologic impairments suggests an occipital lesion. As the onset of the visual field loss was acute, a vascular event (e.g. an ischemic infarct or cerebral hemorrhage) is the most likely etiology for the visual field defect.

The patient needs urgent neuroimaging. If an intracerebral hemorrhage is discovered, there may be a mass effect and shift that might require surgery. However, if the deficit is due to an acute ischemic infarction and the patient otherwise satisfies the criteria for treatment with a tissue plasminogen activator (tPA), a tPA injection would be a consideration as long as the patient and/or her family fully understand and are willing to accept the potential treatment risk of intracerebral hemorrhage (approximately 6.4%). Inclusion criteria for tPA treatment include:

- A clear time of onset of symptoms
- Injection within 3 to 4.5 hours onset of symptoms (defined as the last time the patient was symptom-free) — remember "Time is Brain" (the time window for thrombolytic therapy continues to evolve however)
- Measurable deficit on the National Institute of Health (NIH) stroke scale (NIHSS)
- Patient's age >18 years

Exclusion criteria for tPA treatment include:

- Intracranial hemorrhage or early changes of major infarction on a CT scan
- History of stroke or head trauma in the last 3 months
- Major surgery within last 14 days
- History of intracranial hemorrhage
- Severe hypertension (BP >185/110 mm Hg)
- Rapidly improving or minor symptoms
- Symptoms suggestive of subarachnoid hemorrhage
- Gastrointestinal or urinary tract hemorrhage within last 21 days
- Arterial puncture at non-compressible site within last 7 days
- Seizure at onset of stroke
- Use of oral anticoagulants or heparin
- Recent myocardial infarction
- Protime (PT) >15 seconds
- Platelet count <100,000/mm
- Glucose <50 or >400 mg/dl

The patient needs to have urgent neuroimaging in order to consider tPA treatment. We perform initial cranial non-contrast CT imaging followed by consideration for dynamic CT scanning with CT angiography and CT perfusion studies that rely on rapid rate scanning to follow the passage of an intravenously injected iodinated contrast agent through the cerebral circulation. Reduced cerebral perfusion in the absence of a cerebral blood volume abnormality is indicative of ischemic, yet potentially salvageable, brain tissue. Mismatch can thus be obtained by comparing the size of the cerebral blood volume abnormality with that of the perfusion disturbance. A mismatch implies tissue is at risk.

In this patient, a cranial CT scan revealed no cerebral hemorrhage, but the CT perfusion study (Fig. 2A.2) revealed an area of left occipital ischemia. Therefore, intravenous infusion of tPA would be warranted to attempt to improve her visual field deficit. Patients with cerebral infarct who received a

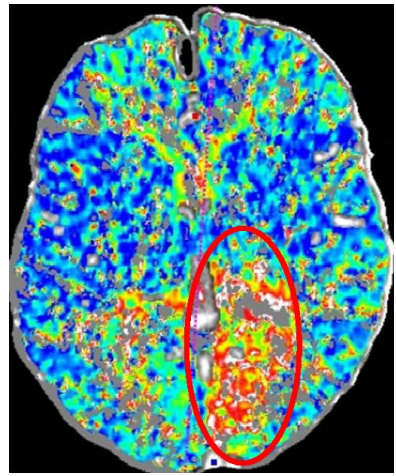

Fig. 2A.2. CT perfusion of the brain demonstrates increased mean transient time in the left posterior cerebral artery distribution consistent with ischemic change (circle).

tPA are at least 30% more likely to have minimal neurologic or no disability at 3 months as compared with those who did not receive treatment. 31% to 50% have complete or near-complete recovery in one year versus 20%–38% of a placebo group.

The treating physician should document in the medical record the reasons for the use or non-use of thrombolytic drugs. If the patient meets the treatment guidelines, and if the treating doctors (e.g. stroke neurologist, ophthalmologist, emergency room physician) or the patient/family chooses not to use thrombolysis, then we strongly recommend that the rationale and the clear discussion of the benefits and risks be documented. Likewise, if the patient does not meet the treatment guidelines, these should be documented as well.

Some facilities have experienced stroke teams available on a 24-hour basis that can perform urgent angiography on ischemic stroke patients. In these centers, intra-arterial tPAs or angioplasty/ stenting or mechanical thrombectomy of the specifically occluded vessel causing the stroke is possible.

If the emergency department concerned does not have adequate coverage by physicians experienced in stroke care and modern technology, there are several options:

- Choose not to accept patients suspected of having stroke and divert them to a nearby stroke center if one is available.
- Upgrade the facility to meet the standards and then accept patients. This requires improving technology, adding experienced stroke clinicians, and facilitating throughput.
- If it is not feasible to divert to a nearby facility, consider connecting with such a facility by telemedicine or consultative arrangements to facilitate care.

Whether or not a tPA is given for the acute infarction, the patient should be admitted to the hospital to further investigate the etiology of the infarction (e.g. a cardiac embolic source, atrial fibrillation, vertebral-basilar atherosclerotic disease, etc.) and to aggressively treat the ischemic risk factor.

Dr. Lee. Like Dr. Brazis, the stroke treatment protocols for reperfusion in acute ischemic stroke (including those producing a homonymous hemianopsia) are at the discretion of the stroke team. Typically, the ophthalmologist is making the diagnosis, ordering the imaging study urgently, and then referring the patient to the stroke service for treatment. The primary acute imaging of choice remains the non-contrast head CT scan to exclude acute hemorrhage or a large volume infarction. Although cranial CT is superior to MRI for acute bleed, a CT scan is not as sensitive as MRI with specialized sequences (e.g. diffusion or perfusion imaging) for acute cerebral ischemia. Unfortunately, reperfusion therapy may be inadvertently given to patients with a "stroke mimic" (e.g. migraine or seizure related Todd's paralysis) and this decision is best left to the experts. Special MRI sequences based upon the restriction of the diffusion of water called diffusion-weighted imaging (DWI) can detect hyperacute ischemic stroke before structural change on CT or traditional structural MRI sequences. In many of my patients who present with an acute, subacute, or unknown duration of a homonymous hemianopsia, the initial cranial CT scan is negative.

If the initial CT is negative, then I typically recommend a cranial MRI with DWI sequences and contrast. If there is evidence for a prior old infarct but no acute infarct (negative DWI), then typically, I will contact the stroke service by phone and let them proceed with an outpatient stroke evaluation at their individual discretion and timing rather than admit the patient.

CHAPTER · 2B

Acute Painful Homonymous Hemianopsia

CASE NO. 2B

A 37-year-old female was reaching up to a high shelf for a pack of cigarettes while at her job at a convenience store when she noted the acute onset of severe neck pain. Shortly after the pain developed, she noticed difficulty in seeing. She denied any periocular pain, headaches, weakness, or photophobia. She could not recall any recent prior trauma. She went home "to sleep it off," but upon awakening the next day, she felt worse; she did not think that her vision was clear to the left side in both eyes.

Ocular examination showed a visual acuity of 20/20 OU. There was no relative afferent pupillary defect, ptosis, or anisocoria. Ocular motility was full. Fundus examination was normal OU. Humphrey visual field showed an almost complete, congruous, left homonymous hemianopia (Fig. 2B.1).

Discussion

Dr. Lee. The localization of any homonymous hemianopia is a retrochiasmal lesion on the contralateral side. The absence of other neurologic symptoms suggests occipital rather than temporal or parietal lobe localization, but neuroimaging is recommended for clinicoradiologic correlation. The Goldmann visual field demonstrates an almost complete, congruous

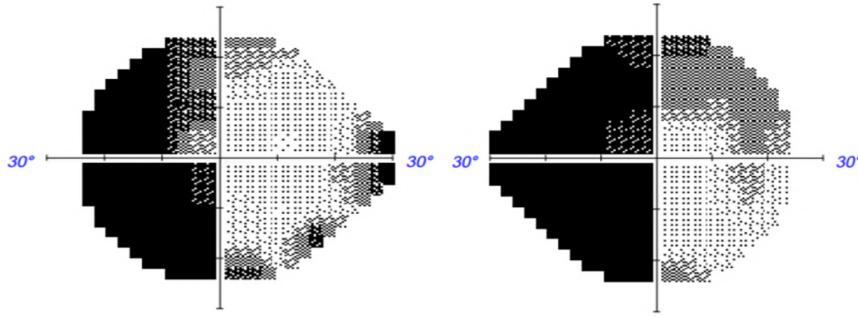

Fig. 2B.1. Humphrey visual field showed a left congruous homonymous hemianopia.

homonymous hemianopia without macular sparing or temporal crescent sparing. The acute onset suggests a vascular event (stroke or hemorrhage) rather than a neoplastic process or other etiology (but sometimes neoplasms present acutely with hemorrhage or seizure). In a young patient with neck pain, the major concerns would be vertebral arterial dissection with a posterior cerebral artery (PCA) infarct, often due to thromboembolic disease. The first study should be cranial imaging. Typically, in the Emergency Room (ER), a non-contrast CT scan of the head would be the first line imaging study, followed by an MRI if the initial head CT was negative. DWI that demonstrates restricted diffusion of water (bright signal on DWI with matched dark signal on an apparent diffusion coefficient or ADC map) in an acute stroke might be useful. Concomitant MRA of the head and neck might be useful to evaluate vascular abnormalities at the same time as the MRI. Admission to the hospital would be recommended if the patient had imaging evidence for an acute stroke.

Dr. Brazis. The patient needs urgent neuroimaging. However, if the deficit is due to an acute ischemic infarction, the patient does not satisfy the criteria for the injection of a tPA because she is already beyond the therapeutic window for the use of this agent.

Course. Cranial MRI/MRA (Fig. 2B.2) showed a subacute infarction of the right PCA territory on DWI. Subsequent catheter angiography showed a

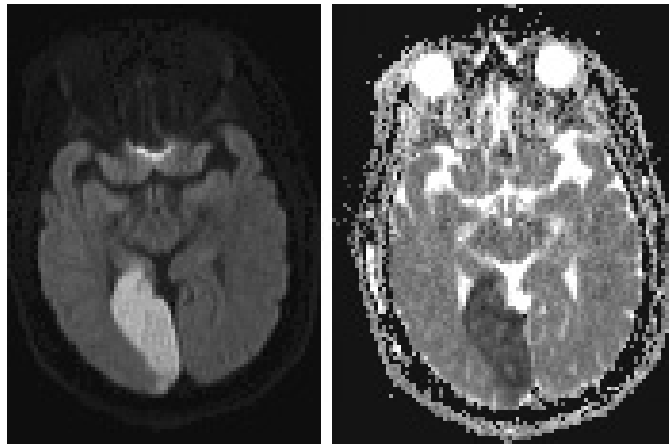

Fig. 2B.2. Diffusion-weighted imaging on MRI shows restricted diffusion (bright signal on right with dark signal on a matched (ADC) map consistent with a right PCA distribution infarct).

subtotal occlusion of the right vertebral consistent with a vertebral artery dissection. The patient was admitted to the stroke service and did well on antiplatelet therapy. The visual field loss, however, did not recover.

Practice Essentials

Visual field defects can be used to localize lesions. The localization of a homonymous hemianopia is a retrochiasmal lesion on the contralateral side. The absence of other neurologic symptoms suggests occipital rather than temporal or parietal lobe localization.

In many of my patients who present with an acute, subacute, or unknown duration for a homonymous hemianopsia, the CT scan is the initial imaging study to be performed.

If the initial CT is negative, a brain MRI with DWI sequences and contrast should be considered if available. If there is evidence for a prior old infarct but no acute infarct (negative DWI), I will typically contact the stroke service by phone and let them proceed with an outpatient stroke evaluation at their individual discretion and timing rather than admit the patient.

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CHAPTER · 3A

Acute Bilateral Optic Disc Edema

CASE NO. 3A

A 31-year-old white female with a body mass index of 40 kg/m^2 presented in the Emergency Room (ER) complaining of bilateral blurry vision for the previous two days. She also related mild headaches for the previous week. Past medical history was unremarkable. Her only medication was birth control pills. Family history was non-contributory.

On examination, the patient's visual acuity was 20/60 OD and 20/80 OS. Confrontation visual fields were normal in both eyes. The pupillary examination was normal without a relative afferent pupillary defect. Ocular motility was full. Slit lamp examination was unremarkable. Intraocular pressure was 12 mm Hg in each eye. Ophthalmoscopy showed bilateral optic nerve edema (Fig. 3A.1). The macula, vessels, and periphery were within normal limits.

Discussion

Dr. Brazis. All patients with papilledema require a thorough urgent neurologic and neuro-ophthalmologic history and physical examination (including blood pressure measurement). In general, the syndromes causing increased intracranial pressure (ICP) include:

- Primary causes
    - Idiopathic pseudotumor cerebri syndrome (idiopathic intracranial hypertension) with or without papilledema

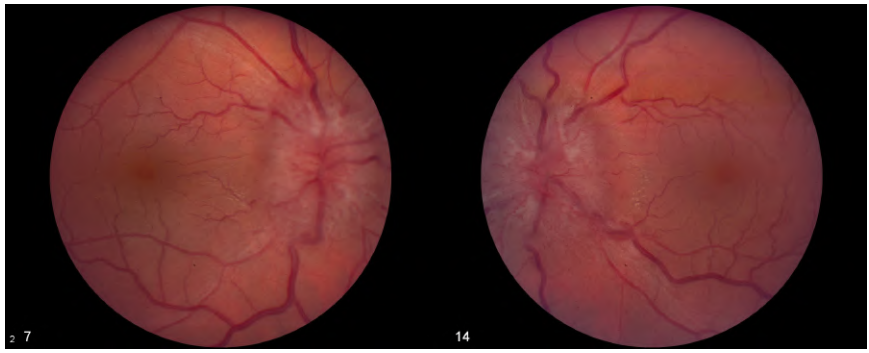

Fig. 3A.1. Fundus photography showing grade IV optic nerve edema bilaterally.

- Secondary causes
  - Hydrocephalus
  - Shunt failure in patient with hydrocephalus (ventriculomegaly may be absent)
  - Mass lesions — tumor, hemorrhage, large infarction, abscess
  - Meningitis/encephalitis
  - Subarachnoid hemorrhage
  - Trauma
  - Arteriovenous malformations (AVMs) with high blood flow overloading venous return
  - Intracranial (e.g. cerebral venous sinuses) or extracranial (e.g. internal jugular) venous obstruction
  - Secondary pseudotumor cerebri syndrome due to certain systemic diseases or drugs (e.g. tetracyclines)

In all patients with bilateral optic disc swelling, the blood pressure should be checked to evaluate for possible hypertensive emergency (i.e. malignant hypertension). Blood dyscrasia should be considered if there are other suggestive retinal vascular findings (e.g. incomplete or complete central retinal vein occlusion with optic disc edema).

Neuroimaging is required in all patients. Cranial CT imaging is the preferred study in evaluating acute vascular processes (e.g. subarachnoid, epidural,

subdural, or intracerebral hemorrhage, acute infarction) or in acute head trauma (e.g. rule out fracture, acute bleed). CT scan may be used in patients with contraindications to MR imaging (e.g. non-MRI compatible pacemakers, ferromagnetic metallic clips in head, metallic foreign bodies) and markedly obese or claustrophobic patients who cannot have an MRI. Otherwise, MR imaging is the modality of choice in papilledema. MR angiography (MRA) or MR venography (MRV) may be useful for suspected arterial disease or venous obstruction. If neuroimaging shows no structural lesion or hydrocephalus, then lumbar puncture is warranted. Studies should include an accurate opening pressure, cerebrospinal fluid (CSF) cell count and differential, glucose, and protein. Additional CSF studies, including cytology, syphilis testing, and other appropriate studies for microbial agents, may also be performed.

Patients with a history of a ventriculoperitoneal shunt for hydrocephalus may develop papilledema, visual loss, or signs of a dorsal midbrain syndrome due to shunt failure. Usually CT or MR imaging reveals recurrence of the hydrocephalus. Shunt malfunction may occur without ventriculomegaly, perhaps due to poor ventricular compliance and "stiff ventricles." Shunt failure should thus be considered when there are signs or symptoms of increased ICP in a shunted patient, even if ventriculomegaly is absent, in order to prevent deterioration of visual function and potentially irreversible visual loss.

Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension (IIH), is a diagnosis of exclusion, and the modified Dandy criteria include:

- Normal neuroimaging studies (usually MRI and MRV)
- Normal cerebrospinal fluid contents
- Elevated opening pressure
- Signs and symptoms related only to increased ICP (e.g. headache, papilledema, nonlocalizing sixth nerve palsy).

PTC is usually idiopathic but may be secondary due to certain systemic diseases, drugs, pregnancy, and intracranial or extracranial venous obstruction. Obstruction or impairment of intracranial venous drainage may result in

cerebral edema with increased ICP and papilledema. Tumors or vascular malformations that occlude the superior sagittal sinus or other cerebral venous sinuses may also cause increased ICP. Septic or aseptic thrombosis or ligation of the cavernous sinus, lateral sinus, sigmoid sinus, or superior sagittal sinus may mimic PTC. Ligation of one or both jugular veins (e.g. radical neck dissection), thrombosis of a central intravenous catheters in the chest or neck, compression of the jugular vein, hemodynamically significant left-to-right cardiac shunt from a cardiac septal defect, subclavian vein catheterization and arteriovenous fistula, the superior vena cava syndrome, or a glomus jugulare tumor impairing venous drainage may also cause increased ICP. Osteopetrosis causing obstruction of venous outflow at the jugular foramen has also been reported, and depressed skull fracture with compression of the venous sinuses are other rare causes of increased ICP.

Cerebral venous sinus thrombosis (CVST) may be the mechanism for PTC reported in several conditions, including systemic lupus erythematosus, essential thrombocythemia, protein S deficiency, antithrombin III deficiency, antiphospholipid antibody syndrome, activated protein C resistance, paroxysmal nocturnal hemoglobinuria, Behçet disease, meningeal sarcoidosis, lymphoma, hypervitaminosis A, mastoiditis, Lyme disease, and trichinosis.

CVST can present with all of the classic criteria for idiopathic PTC, including normal neuroimaging (CT or MRI) and CSF contents. In one study of 160 consecutive patients with CVT, 59 patients (37%) presented with isolated intracranial hypertension. Neuroimaging revealed the involvement of more than one venous sinus in 35 patients (59%); CT imaging was normal in 27 of 50 patients (54%). The superior sagittal sinus was involved in 32 patients (54%) (isolated in seven) and the lateral sinus in 47 (80%) (isolated in 17). The straight sinus was thrombosed in eight patients, cortical veins were involved in two, and deep cerebral veins in three, always in association with thrombosis in the superior sagittal sinus or lateral sinuses. Etiologic risk factors included local causes (7), surgery (1), inflammatory disease (18), infection (2), cancer (1), postpartum (1), coagulopathies (11), and oral contraception (7). The cause

was unknown in 11 cases (19%). The authors emphasized that MRI and MRV should be considered in presumed isolated intracranial hypertension.

Increased blood flow and venous hypertension have also been implicated as the mechanism of papilledema noted in some patients with cerebral AVMs, especially dural AVMs and fistulas. PTC may also occur in association with the Chiari I malformation.

Many systemic diseases, drugs, vitamin deficiencies and excesses, pregnancy, and hereditary conditions have been associated with secondary PTC. In general, many of these reported associations may be coincidental and anecdotal. The etiologies most firmly associated include:

- **Drugs:** Hypervitaminosis A, steroid withdrawal, anabolic steroids, lithium, nalidixic acid, the insecticide chlordecone (Kepone), isoretinoin, ketaprofen (Orudis) or indomethacin in Bartter's syndrome, thyroid replacement in hypothyroid children, danazol, all-transretinoic acid (ATRA) or isotretinoin or tretinoin, cyclosporine, exogenous growth hormone, tetracycline, and minocycline.
- **Systemic diseases:** Behçet syndrome, renal failure, Addison disease, hypoparathyroidism, systemic lupus erythematosus, sarcoidosis.

In this patient, MRV revealed occlusion of the superior sagittal sinus (Figs. 3A.2 to 3A.4), perhaps induced by her birth control pills. A thrombotic profile to investigate for the presence of a prothrombotic state and a pregnancy test are indicated.

Some cases of PTC secondary to venous sinus obstruction may be successfully treated using angioplasty with venous sinus stenting or thrombolytic infusion to improve the venous outlet obstruction. Some authorities suggest anticoagulation. In all cases, if the papilledema persists, other treatments to protect vision should be considered, including surgical procedures such as optic nerve sheath fenestration, ventriculo-peritoneal shunt, or lumboperitoneal shunt.

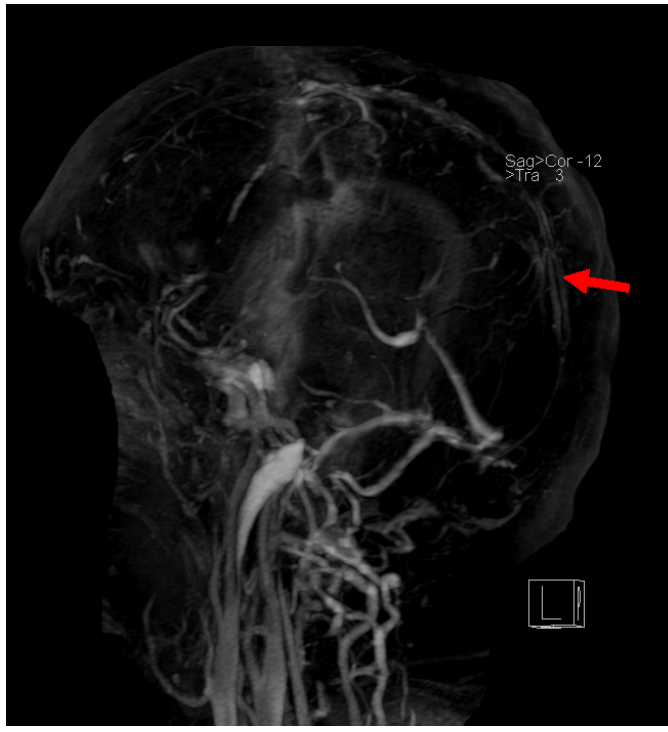

Fig. 3A.2. MR venogram pos contrast demonstrates occlusion of the superior sagittal sinus (arrow).

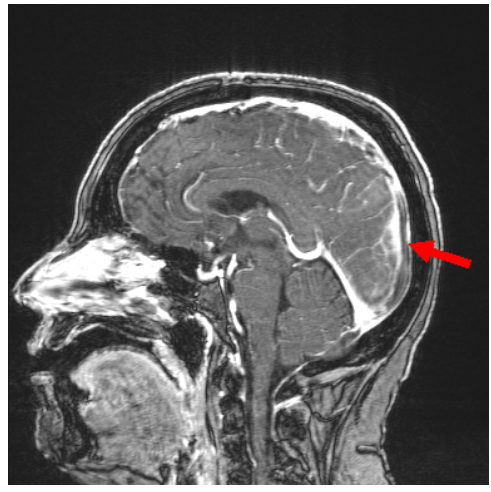

Fig. 3A.3. Brain MRI sagital T1 pos contrast demonstrates the absence of contrast in the superior sagittal sinus (arrow) consistent with the blood clot.

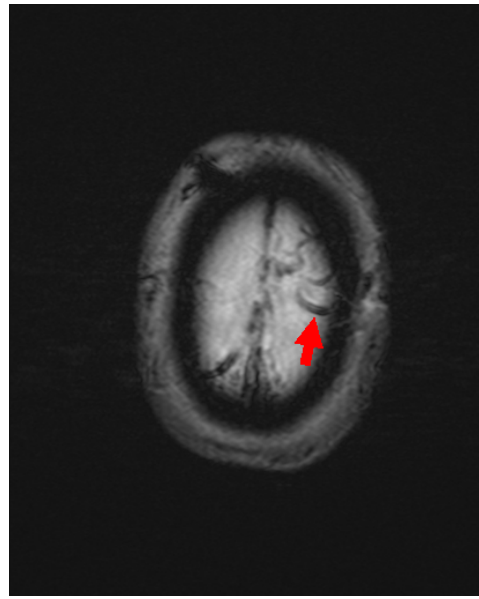

Fig. 3A.4. Brain MRI axial gradient demonstrates a decreased signal within the cortical vein (arrow) consistent with the clot.

Dr. Lee. My typical approach to a patient with papilledema is to look for an exogenous cause in the history (e.g. medication-induced PTC as described by Dr. Brazis above), assess for risk factors for cerebral venous sinus thrombosis (e.g. clotting disorders, trauma) and check the systemic blood pressure. In patients who fit the "demographic profile" for PTC (e.g. obese young female with signs and symptoms confined to those related to increased ICP), I then proceed with a cranial MRI and contrast MRV to rule out CVST. If the MRI and MRV are negative, then I proceed to a lumbar puncture to check the CSF contents and to measure the opening pressure. I almost always initially treat patients with papilledema due to PTC with acetazolamide (Diamox) unless there is a contraindication. I perform a typical complete eye exam, a formal visual field, and document their baseline with fundus photography. Some obese female patients come to me with a previously performed normal contrast MRI but no MRV. In these patients, assuming they have no other atypical signs or symptoms, I will obtain the lumber puncture (LP) to confirm the diagnosis and treat as PTC. If they fail to respond appropriately or if they are not the

typical PTC demographic (e.g. male, thin, elderly), I will ask the patient to undergo a contrast MRV to rule out sinus thrombosis, but an MRV could be performed in every patient, especially as more and more patients have an increased BMI at baseline in the United States. Unlike a typical idiopathic PTC patient who can be treated as outpatients generally, CVST patients usually require hospitalization, and I contact my stroke neurology colleagues in this regard for decision making on admission and inpatient medical treatment.

CHAPTER · 3B

Subacute Bilateral Optic Disc Edema

CASE NO. 3B

A 24-year-old woman presented with a six-week history of bifrontal headaches, pulse-synchronous tinnitus, and transient visual obscurations (TVOs) lasting seconds at a time OU. She rated her headache as severe (10/10 scale) and she was taking regular acetaminophen and ibuprofen for pain control without relief. The headaches were worse in the morning and when leaning forward. The TVOs were worse with bending over and seemed to be occurring more frequently. She has been feeling nauseated over the past two weeks, but there were no additional neurological symptoms. Her vision has been getting blurred over the last 10 days and has deteriorated over the past 48 hours. She admits to a 52 lb weight gain over the past three months, which had occurred after the birth of her last child. Her current height was 5'5" and she weighed 312 lb.

There was no significant past medical history and there was no positive family history of headaches. She was not allergic to any medication, and other than oral analgesics, she was not on any regular medication. She specifically denied the use of tetracyclines, lithium, vitamin A analogs, or corticosteroids (typically withdrawal from steroid treatment).

Examination revealed a moderately obese young woman. The blood pressure was 130/85 mm Hg. Visual acuity was 20/20 OU. She had no diplopia and there was no evidence for sixth nerve palsy on exam. Fundus examination (Figs. 3B.1 and 3B.2) showed severe optic nerve head edema. OCT and visual fields are shown in Fig. 3B.3 and Fig. 3B.4, respectively.

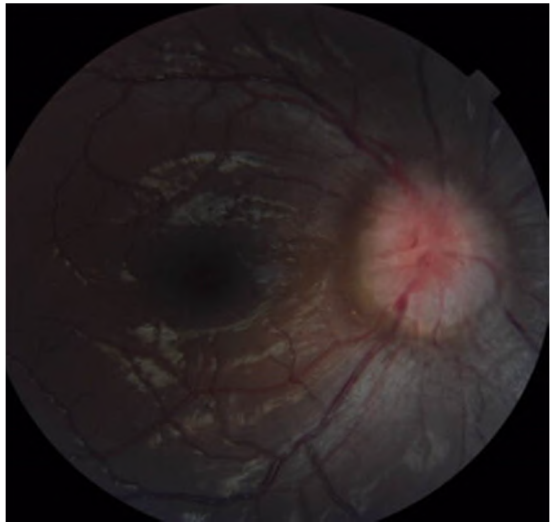

Fig. 3B.1. Color picture of the right fundus showing grade 4 optic disc swelling.

Fig. 3B.2. Color picture of the left fundus showing grade 4 optic disc swelling.

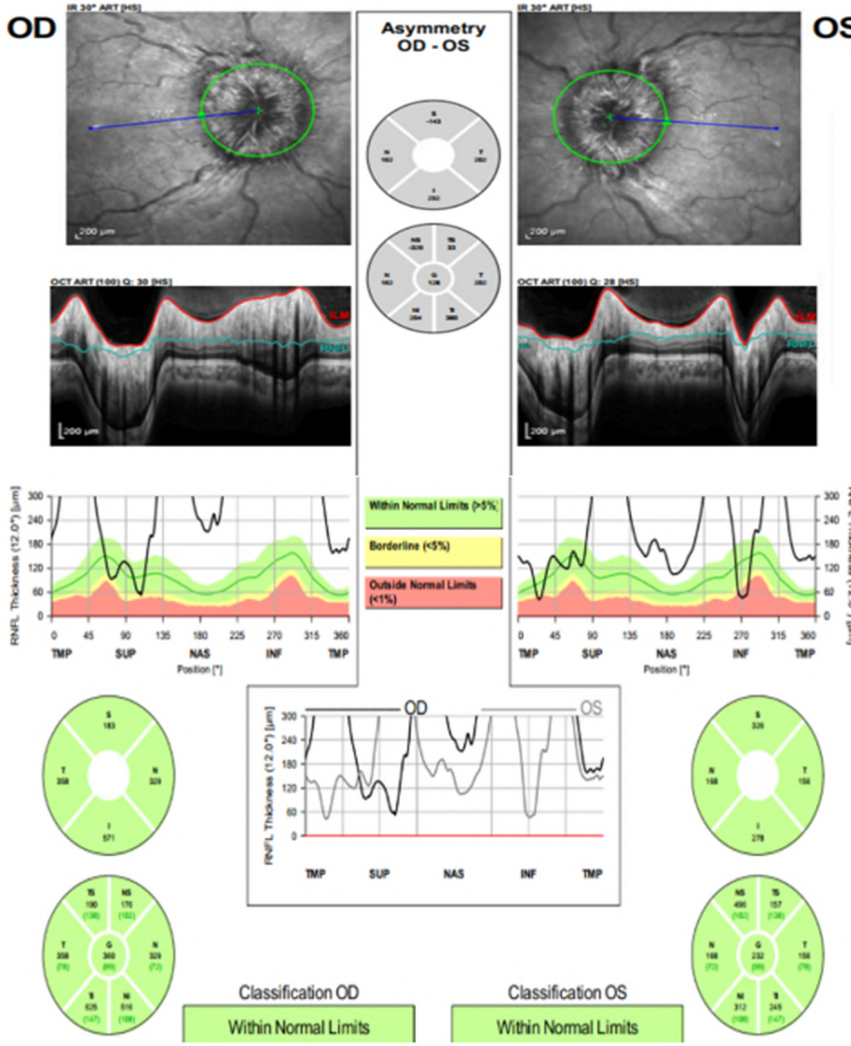

Fig. 3B.3. Optic nerve head OCT showing gross bilateral swelling of the optic nerve heads.

Discussion

Dr. Lee. Bilateral optic disc edema in the setting of headache, TVOs, and pulse synchronous tinnitus (PST) should be considered to be papilledema until proven otherwise. The clinician is encouraged to limit the use of the term "papilledema" for optic disc edema related to increased ICP. This will avoid

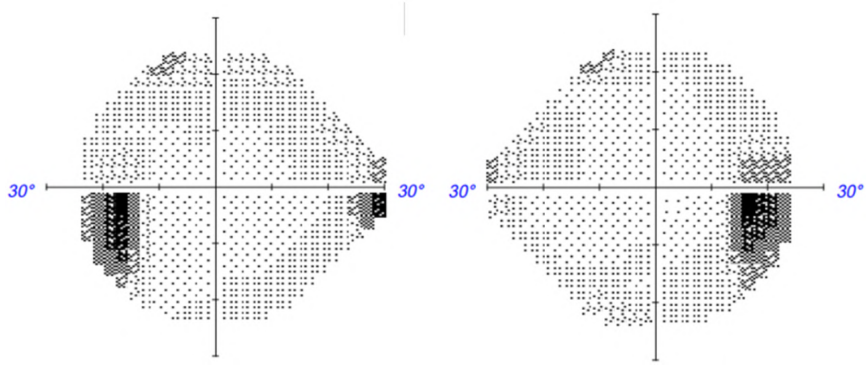

Fig. 3B.4. Humphrey visual field showing enlargement of the blind spot in both eyes with mild inferior nasal scotoma in the left eye.

miscommunication with other physicians. In an obese female, the diagnosis of idiopathic PTC should be considered as the leading diagnosis.

As noted above, I recommend neuroimaging (e.g. contrast MRI with MRV) and an LP to confirm the diagnosis of idiopathic PTC by modified Dandy criteria. I recommend medical therapy with acetazolamide (Diamox) as our first line treatment. Other diuretics and other medical treatments can be used as adjunctive treatments (e.g. furosemide, topirimate) but acetazolamide is my preferred first line agent and has demonstrated clinical safety and efficacy in the Idiopathic Intracranial Hypertension Treatment Trial (IIHT). If patients fail, are intolerant to, or are non-compliant with maximum medical therapy, consideration could then be given for surgical treatment (e.g. optic nerve sheath fenestration [ONSF], venous sinus stenting, or intracranial shunting procedure). I tend to favor ONSF for patients with visual loss as their predominant complaint and shunting or stenting procedures for those with headache or headache with severe visual loss as their predominant complaint. The choice between a lumboperitoneal shunt (LPS) and a stereotactic ventriculoperitoneal shunt (VPS) with or without a programmable valve must be made on an individual and institutional basis, depending on local availability and expertise with each procedure. Likewise for venous sinus stenting versus CSF shunting procedures. In patients such as this case who present with visual

loss, the etiology for the visual loss should be carefully established. Patients with severe visual field loss or central acuity loss (not attributable to macular fluid or hemorrhage) should be considered for emergent surgical intervention (e.g. ONSF, stent, LPS, or VPS). The most common errors made in patients with IIH include not excluding alternative etiologies especially in patients who do not fit the typical IIH profile (e.g. thin patients, males, elderly or children) and ordering the wrong or inadequate neuroimaging study (I recommend contrast cranial MRI and MRV unless there is a contraindication). A CT with CT venogram is sometimes a necessary alternative imaging choice for patients who cannot have an MRI (e.g. pacemaker, severe claustrophobia, metallic foreign body, etc.).

Dr. Brazis. I agree with Dr. Lee that idiopathic PTC is a diagnosis of exclusion. The modified Dandy criteria include: 1) normal neuroimaging studies (usually MRI), 2) normal CSF contents, 3) elevated opening pressure, and 4) signs and symptoms related only to increased ICP (e.g. headache, papilledema, nonlocalizing sixth nerve palsy). PTC is usually idiopathic but may be due to certain systemic diseases, drugs, pregnancy, and intracranial or extracranial venous obstruction.

I recommend that patients with PTC undergo MR imaging of the head. Atypical patients should undergo MR venography to evaluate for venous occlusive disease, but we recommend cerebral angiography only in select cases. If venous occlusive disease is discovered, then evaluation for a hypercoaguable state and vasculitis should be performed.

My indications for surgical treatment (usually ONSF, venous stenting, or ventriculoperitoneal shunt) for PTC include:

- New worsening visual field defect[a]
- Enlargement of previously existing visual field defect[a]
- Reduced visual acuity not due to macular edema

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[a] Blind spot enlargement should not be considered significant visual loss (refractive).

- Presence of severe visual loss (20/40 or worse) in one or both eyes at the time of initial examination
- Anticipated hypotension induced by treatment of high blood pressure or renal dialysis
- Psychosocial reasons, such as the patient's inability to perform visual field studies, noncompliance with medications, an itinerant lifestyle
- Headache unresponsive to standard headache medications

Course. A cranial MRI with contrast MRV demonstrated an empty sella and the edematous nerve heads were also visible (Figs. 3B.5 and 3B.6). There was no evidence for cranial venous sinus thrombosis. A lumbar puncture showed an opening pressure of 30 cm of water but normal CSF contents. The patient was started on acetazolamide 500 mg TID, but the disc edema persisted, and she underwent optic nerve sheath fenestration OD. After surgery, the disc edema improved dramatically.

Fig. 3B.5. Sagittal MRI showing an empty sella.

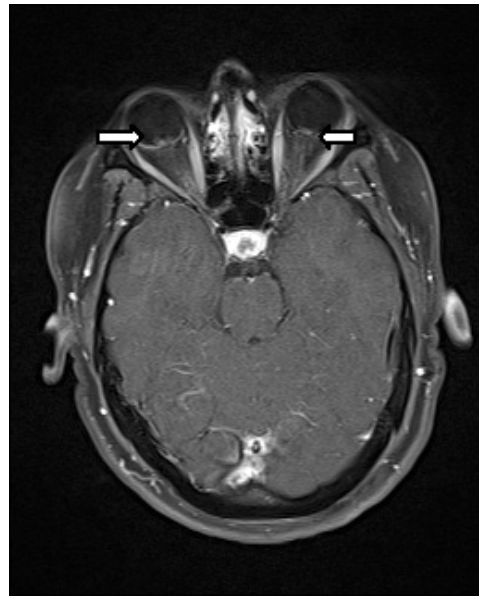

Fig. 3B.6. Axial MRI showing edematous optic discs in both eyes labeled with arrows.

Practice Essentials

— Bilateral optic disc swelling is most commonly caused by IIH; however, this is a diagnosis of exclusion and other secondary causes need to be excluded
— Look for an exogenous cause of increased ICP (e.g., tetracyclines, lithium, vitamin A analogs, or corticosteroid withdrawal)
— Assess for risk factors for cerebral venous sinus thrombosis (e.g. clotting disorders, trauma)
— Check the systemic blood pressure
— Confirm with the modified Dandy criteria for IIH, including: 1) normal neuroimaging studies (usually MRI), 2) normal CSF contents, 3) elevated opening pressure, and 4) signs and symptoms related only to increased ICP (e.g. headache, papilledema, nonlocalizing sixth nerve palsy).

— In patients who fit the "demographic profile" for PTC (e.g. obese young female with signs and symptoms confined to those related to increased ICP), I then proceed with a cranial MRI scan and contrast MRV to rule out CVST, but some cases may require CT/CTV (CT venography).
— Management is made on an individual case-by-case basis. Acetazolamide is a proven therapy in a randomized controlled study (IIHT); however, in the emergency setting, consider the possibility of fulminant IIH, where there is rapid and severe deterioration in visual acuity or visual field, which require surgical intervention.
— Surgical interventions include ONSF; venous sinus stenting, and CSF diversion procedures.

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CHAPTER · 4

Acute Homonymous Hemianopsia in Febrile Patient

CASE NO. 4

A 22-year-old white female presented in the Emergency Room (ER) complaining of high fever and chills after undergoing a piercing in her nose (Fig. 4.1). She also related some difficulty with her vision on her right side. Past medical history was unremarkable. On examination her visual acuity was 20/20 in each eye. Ocular motility was full OU. Pupillary examination was normal. The Humphrey visual field showed an inferior right homonymous hemianopia (Fig. 4.2). Slit lamp examination was unremarkable. Ophthalmoscopy was within normal limits OU.

Discussion

Dr. Brazis. An inferior homonymous quadrantanopia is most often due to a superior occipital lesion or a parietal lesion ("pie on the floor"). In patients with occipital lesions, the visual field defects often occur in isolation, while other localizing signs or parietal involvement are usually evident in patients with parietal lesions. Therefore, although visual field defects may occur in relative isolation with parietal lobe lesions, lesions in this location more often betray themselves by other signs of neurologic dysfunction. Parietal lobe lesions may be associated with contralateral somatosensory impairment, including impaired object recognition, impaired position sense, impaired touch and pain sensation,

Fig. 4.1. External photography showing the nose piercing.

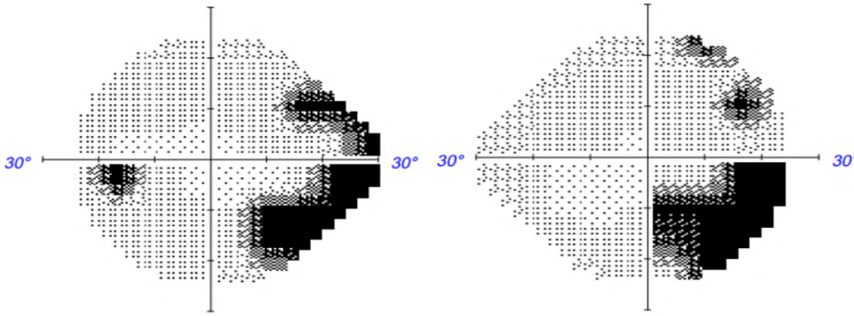

Fig. 4.2. Humphrey visual field showing the inferior right homonymous hemianopia.

and tactile extinction. Dominant parietal lesions may cause apraxia, finger agnosia, acalculia, right-left disorientation, alexia, and aphasic disturbances. Non-dominant lesions may be associated with anosognosia (denial of neurologic impairment), autotopagnosia (failure to recognize hemiplegic limbs as belonging to the self), spatial disorientation, hemispatial neglect, constructional apraxia (abnormal drawing and copying), and dressing apraxia.

In a patient with fever and chills and a visual field defect, one must be concerned about the possibility of an infectious process affecting the central nervous system. Lesions producing such impairment include abscesses,

aneurysms, empyema, encephalitis, granuloma, meningitis, and ischemic infarction related to endocarditis or sepsis.

An abscess is a circumscribed area of pus that may be epidural, subdural, or intracerebral. Intracerebral abscesses are usually solitary and are most often located in the cerebral hemispheres. Most intracranial abscesses are caused either by local invasion of one or more organisms or by septic emboli. An untreated or incompletely treated middle ear infection is the most common source of a locally derived brain abscess. Chronic mastoiditis may produce a brain abscess, as may chronic paranasal sinusitis. Orbital cellulitis may cause intracranial abscesses, but these are usually frontal or temporal in location caused by the extension of the organism through the superior orbital fissure. Acute bacterial meningitis is a rare cause of brain abscess, except in neonates. Septic foci on the scalp or face are relatively a rare cause of brain abscess. Dental infections, tonsillitis, or other facial infections may cause an abscess. Cerebral abscesses may also occur after trauma or neurosurgical procedures. Metastatic abscess seas that result from blood-borne organisms may develop in the setting of bacteremia or septicemia. Such abscesses are usually multiple and may be of varying sizes.

Most intracranial abscesses are caused by bacteria. Aerobic bacteria are found more often than anaerobic bacteria, but polymicrobial infections may exist in a single abscess. The most common aerobic bacteria that produce both single and multiple intracranial abscesses are Gram-positive cocci, such as Streptococcus and Staphlococcus species, and Gram-negative bacilli, including the Haemophilus species and many members of the Enterobacteriaceae. Nevertheless, Gram-negative cocci, such as Neisseria meningitides, and Gram-positive bacilli, such as Listeria monocytogenes, Actinomycosis, and Nocardia, can produce a brain abscess in otherwise healthy people. The most common anaerobic bacteria that cause brain abscesses are the Gram-negative bacilli, Bacteroides, and Propionibacterium. Organisms other than bacteria may produce intracranial abscesses, particularly in chronically ill, immunodeficient, or immunosuppressed patients (e.g. viral, bacterial, fungi, protozoal, and parasitic).

Neuroimaging (e.g. initial cranial CT followed by cranial MRI) is warranted urgently. Suppurative encephalitis appears as an area of decreased density on a CT scan, whereas an abscess appears as a low-density core surrounded by a capsule that enhances when the patient is given an intravenous injection of iodinated contrast agent. Features of an abscess on MRI study include:

- Peripheral edema producing mild hypointensity on T1-weighted images and marked hyperintensity on proton density-weighted and T2-weighted images;
- Central necrosis with abscess fluid that is hypointense relative to white matter and hyperintense relative to CSF on T1-weighted images and hyperintense relative to gray matter on proton density- weighted and T2-weighted images;
- Extraparenchymal spread (intraventricular or subarachnoid) manifested by an increased intensity relative to normal CSF on T1-weighted images, proton density-weighted, and T2 weighted images;
- Visualization of the abscess capsule is iso- or mildly hyperintense relative to the brain on T1-weighted image and iso- to hypointense related to white matter on proton density-weighted and T2-weighted images.

Course. Initial acute brain CT with contrast in our patient demonstrated a ring-enhancing lesion in the left occipital lobe consistent with a brain abscess (Fig. 4.3). Diffusion-weighted imaging (DWI) MRI of the brain demonstrates a high signal in the left occipital region corresponding to the area of ring enhancement, representing pus within the abscess (Fig. 4.4). It was thought that the abscess was due to a hematogenous spread of infection, possibly related to the recent nose piercing.

Dr. Brazis. The treatment of an intracranial abscess is directed both at the abscess and its source and may be medical, surgical, or both.

Medical treatments usually consist of appropriate antibiotics or other drugs designed to eliminate the organism causing the infection. The blood-brain barrier is altered in areas of cerebritis and an abscess, thus allowing increased penetration of anti-infectious agents. Occasionally, corticosteroids are used to

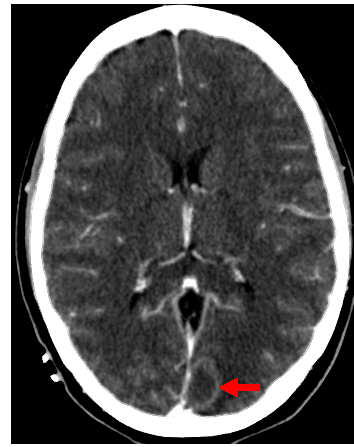

Fig. 4.3. Brain CT with contrast demonstrates the ring lesion in the left occipital lobe (arrow) consistent with a brain abscess.

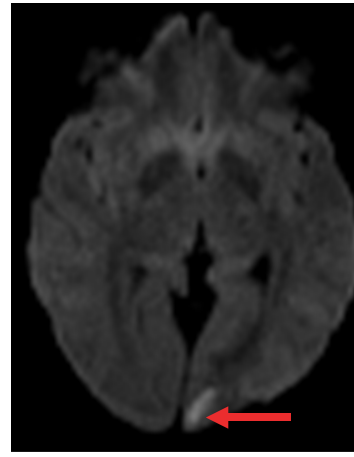

Fig. 4.4. Diffusion-weighted image of the brain demonstrates a high signal in the left occipital region (arrow) corresponding to the area of ring enhancement on the previous image, representing an abscess.

reduce the cerebral edema surrounding the intracranial abscess. The specific medical regimen recommended depends on the known or presumed causative organism. In patients with no significant neurologic deficits with a normal state of consciousness, with a single deep abscess less than 2 cm in diameter, harboring multiple abscesses, or for whom surgery of any type might be inappropriately

hazardous, medical treatment alone may be successful in eradicating the abscess. If there is clinical deterioration, if CT scanning or MR imaging reveals an enlargement of the abscess at any time during medical treatment, or if there is no decrease in the size of the abscess within several weeks, surgery should be considered. Most patients with an intracerebral abscess should undergo aspiration or excision of the abscess for both diagnosis and treatment. Aspiration is usually all that is required. When a brain abscess results from a systemic infection, the source of infection also must be treated (e.g. bacterial endocarditis).

Dr. Lee. An intracerebral abscess can be a life-threatening condition. Although the classic triad of fever, headache, and focal neurologic deficit (e.g. homonymous hemianopsia) are useful findings, these findings do not always occur in patients with a brain abscess. Likewise, an elevated white blood cell count or elevated erythrocyte sedimentation rate is only variably present, if at all, in brain abscess cases. Classically, a ring-enhancing mass lesion on CT or contrast MRI could be an abscess, a primary brain tumor, or a metastasis. Diffusion-weighted imaging (DWI) in a brain abscess might show a hyperintense signal as opposed to the other lesions in the differential, which normally would not be bright on DWI. A patient thought to have a primary brain tumor might undergo a biopsy alone and be discharged pending the pathology if an abscess is not considered ahead of time in the differential diagnosis. The absence of fever, headache, or leukocytosis provides a false sense of security in such patients. The history of piercing in this case is intriguing, and a brain abscess has been associated with tongue piercing.

Practice Essentials

— Homonymous quadrantanopia is most often due to an occipital lesion or a parietal/temporal lesion. In patients with occipital lesions, the field defects often occur in isolation, while other localizing signs or parietal involvement are usually evident in patients with parietal/temporal lesions.
— Febrile patients with homonymous quadrantanopia represent an emergency due to a high suspicion for a brain abscess. Neuroimaging with MRI is warranted, where DWI MRI of the brain demonstrates a

high signal in the left occipital region corresponding to the area of ring enhancement, representing purulence within the abscess.

— Urgent referral to neurosurgery and antibiotic treatment is essential in the management.

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CHAPTER · 5

Acute Painless Isolated Sixth Nerve Palsy

CASE NO. 5

A 66-year-old white man presented in the Emergency Room (ER) complaining of new onset binocular horizontal diplopia, which was painless. He had no other eye complaints. His past medical history was remarkable for hypercholesterolemia controlled with statin therapy. Past medical, social, surgical, and family history were all non-contributory.

On examination, visual acuity was 20/20 OU. Confrontation visual field was normal OU. Pupillary examination was normal without an afferent pupillary defect. Ocular motility showed an isolated cranial nerve VI nerve palsy on the left (Fig. 5.1). There were 25 prism diopters of esotropia in a primary position worse in gaze to the left. Fundus exam was normal OU.

Examination showed a cup-to-disc ratio of 0.3 in each eye. The macula, vessels, and periphery were normal in both eyes.

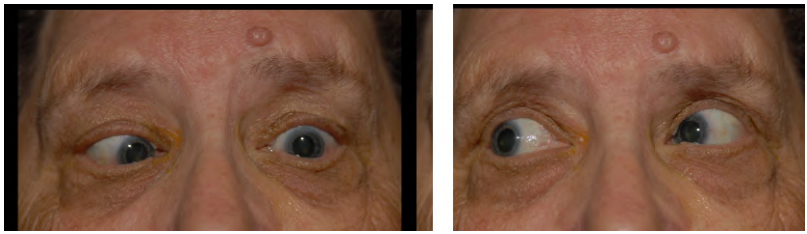

Fig. 5.1. Ocular motility photography showing the incomitant esotropia and the left abduction deficit in left gaze consistent with the left VI nerve palsy. Right gaze is normal.

Discussion

Dr. Brazis. Based on topographic anatomy, sixth nerve palsies (SNPs) may be divided into isolated SNPs and non-isolated SNPs. The criteria for the diagnosis of an isolated SNP include:

- An ipsilateral abduction deficit
- Incomitant esodeviation that is typically worsened with gaze into the field of the weak lateral rectus muscle (but may become comitant over time)
- Exclusion of Duane's retraction syndrome, spasm of the near reflex, and other causes of abduction deficits that can mimic an SNP, and exclusion of patients with signs of the following:
    - Orbital disease (e.g. chemosis, proptosis, lid swelling, injection, and positive forced ductions)
    - Myasthenia gravis (e.g. ptosis, Cogan lid twitch sign, orbicularis oculi weakness, muscle fatigue or variability)
    - Multiple cranial nerve palsies (including bilateral SNP) or radiculopathy
    - Brainstem signs (e.g. Horner syndrome, hemiplegia, cerebellar signs)
    - Systemic, infectious, or inflammatory risk factors for an SNP (e.g. history of previous malignancy, giant cell arteritis, collagen vascular disease)
- Exclusion of patients with severe headache

There are a number of types of SNPs that help to differentiate etiology and guide the management of SNP.

Type 1: Non-isolated SNP

- SNPs are considered non-isolated in the presence of the exclusionary conditions outlined above.

Type 2: Traumatic SNP

- Isolated unilateral SNPs, which have a clearly established temporal relationship to significant previous head trauma and do not progress, are considered traumatic in origin. Patients with SNP following minor head trauma are excluded.

Type 3: Congenital SNP

- Patients born with SNP or noted to have an SNP within the first three months of life.

Type 4: Vasculopathic SNP

- Vasculopathic SNP occurs in patients older than 55 years or those with known ischemic risk factors (e.g. hypertension or diabetes).

Type 5: Nonvasculopathic SNP

- Patients without vasculopathic risk factors defined above are considered to have nonvasculopathic SNP.

Type 6: Progressive (non-isolated) or Unresolved SNP

- SNPs that worsen after the acute stage (greater than two weeks) as defined by a significant increase in the measured ocular deviation or who develop new neurologic findings are considered progressive or non-isolated. Patients without resolution in the measured horizontal deviation after 12 to 16 weeks are considered unresolved.

The first clinical step is to determine whether SNP is indeed occurring in isolation. Sixth nerve nuclear lesions involve projections to the contralateral third nerve nucleus via the medial longitudinal fasciculus (MLF) and, therefore, cause

horizontal gaze palsy rather than an isolated abduction deficit. An ipsilateral facial palsy may also occur because of the close proximity of the facial and abducens nerve in the pons. Nuclear lesions are usually associated with other brainstem signs (e.g. hemiparesis, hemisensory loss, a central Horner syndrome). Likewise, lesions of the sixth nerve fascicle involve adjacent structures (e.g. cranial nerves V, VII, and VIII; cerebellar ataxia; a central Horner syndrome; or contralateral hemiplegia). Patients with presumed nuclear (horizontal gaze palsy) or fascicular SNP should undergo neuroimaging (usually MR imaging) directed to the pons.

Lesions of the sixth nerve in the subarachnoid space may result in unilateral or bilateral SNP. This SNP can be a nonlocalizing finding due to increased intracranial pressure (ICP) from any etiology. Patients with a subarachnoid space lesion should undergo neuroimaging directed to this location, followed by a lumbar puncture as needed.

Lesions of the petrous apex causing SNP are associated with other neurologic findings, including involvement of other cranial nerves (e.g. fifth, seventh, and eighth) or facial pain. Neuroimaging should be directed toward the petrous apex (cranial MRI or CT for bone involvement).

With lesions of the cavernous sinus, SNPs usually occur in association with other cranial neuropathies (e.g. third, fourth, or fifth nerves) or a Horner syndrome. Neuroimaging (usually MR imaging) should be directed to the cavernous sinus in such cases.

Lesions of the orbit causing SNP are usually associated with other orbital signs such as proptosis or chemosis. Neuroimaging (preferably MR imaging) should be directed to the orbit.

Our patient had no history of a congenital SNP, had no history of recent trauma, and clinically has an isolated SNP. The patient may well have a vasculopathic (ischemic) SNP. Isolated vasculopathic SNP (Type 4) may be observed (without neuroimaging) for improvement for four to 12 weeks. Some authors have recommended observing vasculopathic isolated SNP beyond a

three-month interval of recovery if the esotropia and the abduction deficit were decreasing. Elderly patients who present with an isolated SNP and headache, scalp tenderness, jaw claudication, or visual loss should undergo an appropriate evaluation for giant cell arteritis. We recommend erythrocyte sedimentation rate and, when clinically indicated, a temporal artery biopsy. Patients with progression or lack of improvement (Type 6) should undergo MRI neuroimaging.

It should be noted that early progression of paresis over one week in vasculopathic SNP is not uncommon. We do not consider progression over the first week after onset to be a sign of nonvasculopathic SNP.

I recommend that patients with nonvasculopathic SNP (Type 5) undergo neuroimaging. Younger patients, or those without vasculopathic risk factors (Type 5), could also undergo a more extensive evaluation, including a fasting blood glucose, complete blood cell count, and blood pressure check for underlying vasculopathy. Other testing, including neuroimaging (MR) and, if necessary, a lumbar puncture, are recommended. Type 5 SNPs have a significant (27%) chance of harboring an underlying malignant neoplasm. Evaluation for myasthenia gravis should also be considered in these patients. Testing for vasculopathic risk factors in Type 4 or Type 5 SNP patients should be performed, even in the absence of a previous history of diabetes or hypertension. Ocular motor cranial neuropathies may be the presenting or only sign of underlying vasculopathy in these patients.

Patients with progressive or unresolved SNPs (Type 6), or patients with new neurological signs or symptoms, should undergo neuroimaging. Progressive or unresolved SNP patients should have neuroimaging. In a study of 13 chronic SNPs, four were idiopathic, four were due to tumors, two were traumatic, one was postspinal anesthesia, one was due to temporal arteritis, and one was due to an intracavernous aneurysm. In this study, "chronic" was defined as an SNP lasting six months or longer. In another review of 38 patients with chronic SNP, 14 (37%) were discovered to have an intracranial lesion. These authors specifically recommended neuroradiologic investigation at onset in any patient with a history of carcinoma.

Aneurysm is a rare cause of acquired SNP. We do not typically recommend evaluation for an aneurysm in isolated SNP but an aneurysm can cause SNP in patients with signs of subarachnoid hemorrhage, papilledema, or other cranial neuropathies.

Dr. Lee. The traditional teaching is that an isolated SNP in a vasculopathic patient that is resolving or has resolved does not need neuroimaging or other evaluation besides treatment of the vasculopathic risk factors. Some authors, given the low risk of MRI, disagree however with this "traditional" teaching. In several papers, a low but not zero-rate of treatable etiologies (e.g. meningioma, brainstem ischemia, demyelinating disease) has been discovered through imaging at onset. Although I recognize the results of these studies, I do not believe that there is any single correct answer to the question of imaging. It has been my experience that vasculopathic patients with SNP who are also harboring an underlying nonischemic intracranial etiology either have non-neurologically isolated SNP or do not improve over the observational period and, therefore, will eventually undergo the appropriate imaging study. In these patients with meningiomas and other chronic lesions, the short delay in the diagnosis does not generally change management. Nevertheless, neuroimaging is a reasonable approach for SNP regardless of vasculopathic risk factors.

On the other hand, chronic SNP is a well-known "harbinger" of serious and potentially treatable intracranial disease. I image with a cranial MRI with contrast and with constructive interference in steady state (CISS) sequences to follow the entire course of the sixth cranial nerve. Patients who worsen, do not improve, are not isolated, or who develop new neurologic signs and symptoms should undergo evaluation, including neuroimaging for alternative etiologies for the SNP.

Practice Essentials

— SNP mostly present with an inward deviation of one eye (also known as esotropia), with limited abduction in the affected eye.
— The most common cause of SNP is small vessel disease. Such a diagnosis should not be given if the symptoms and signs do not improve with time

(usually weeks to few months) or if signs of other nerve palsy exist. In such cases, neuroimaging is warranted.

— The imaging choice is a brain MRI with contrast and with CISS sequences to follow the entire course of the sixth cranial nerve.

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CHAPTER · 6

Acute Progressive Bilateral Ophthalmoplegia with Mental Status Change

CASE NO. 6

A 33-year-old man was brought to the Emergency Room (ER) because of a change in his mental status. His wife related that the patient was fine the previous day. However, on that day that he was brought in for evaluation, she noticed his confusion. His past medical history was remarkable for hypertension controlled with hydrochlorothiazide and high cholesterol controlled with diet and exercise.

On examination, the patient was somnolent and also confused on attempts to measure his visual acuity. The ocular motility showed a limitation of upgaze. Pupillary examination showed light-near dissociation of the pupils OU. Slit lamp examination and funduscopic examinations were within normal limits.

Discussion

Dr. Brazis. The acute onset of mental status changes and ocular signs is most consistent with a cerebral infarct or hemorrhage. The impairment of upward gaze and the light-near dissociation of the pupils may be localized to the dorsal midbrain. With the dorsal midbrain syndrome, there is impairment of all upward eye movements (although the vestibuloocular reflex and Bell's

phenomenon may sometimes be spared). Downgaze saccades and smooth pursuit may be impaired, but downward vestibuloocular movements are spared.

Downbeating nystagmus may be present. The upper eyelid may be retracted, baring the sclera above the cornea (Collier "tucked lid" sign); this sign is probably due to damage to posterior commissure levator inhibitory fibers. Bilateral ptosis may result when the lesion extends ventrally to involve the caudal central nucleus of cranial nerve III. The pupils are large and react poorly to light, but the near response is spared (light-near dissociation). Occasionally, skew deviation with the higher eye on the side of the lesion is noted. Convergence and divergence are often impaired. In some patients, convergence spasm may result in slow or restricted abduction ("mid-brain pseudo-sixth") during horizontal refixations. Attempted upgaze may result in convergence-retraction nystagmus, with quick adducting-retraction jerks. This phenomenon can be elicited at the bedside by having the patient watch a downward-moving optokinetic drum. In this case, the normal upward corrective saccades are replaced by convergence-retractory nystagmus, which is made up not by convergence movements but by opposed adducting saccades, at least in some cases. The retraction of the eye into the orbit results from irregular co-firing of several extraocular muscles, perhaps due to impairment of recurrent inhibition with the oculomotor subnuclei or abnormal vergence activity. Fixation instability with square-wave jerks may also be noted.

Tumors are most often responsible for damage of the dorsal midbrain. Hydrocephalus is another common etiology, especially when dilation of the third ventricle and aqueduct or enlargement of the suprapineal recess causes pressure on and deformity of the posterior commissure. Patients with shunted hydrocephalus may develop features of the pretectal syndrome with shunt dysfunction even without any dilation of the ventricular system or elevation of intracranial pressure; thus, the observation of these clinical features provides a sensitive index of shunt dysfunction regardless of ventricular size or isolated measurements of intracranial pressure. Less common causes of pretectal syndrome include thalamic or midbrain hemorrhage or infarction, hypoxia, multiple sclerosis, trauma, lipid storage diseases, Wilson disease, drugs (e.g.

barbiturates, carbamazepine, neuroleptics), Whipple's disease, syphilis, and tuberculosis. Upward gaze is often limited in Parkinson's disease and may be rarely affected with vitamin B12 deficiency.

Occlusive vascular disease of the rostral basilar artery, usually embolic, frequently results in the "top of the basilar" syndrome due to infarction of the midbrain, thalamus, and portions of the temporal and occipital lobes. This syndrome may also occur in patients with giant basilar artery tip aneurysms, in patients with vasculitis, and after cerebral angiography. This syndrome variably includes:

- Disorders of eye movements: Unilateral or bilateral paralysis of the upward or downward gaze, disordered convergence, pseudo-abducens palsy, convergence-retraction nystagmus, ocular abduction abnormalities, elevation and retraction of the upper eye-lids (Collier's sign), skew deviation, and lightning-like eye oscillations.
- Pupillary abnormalities: Small and reactive, large or midposition and fixed, light-near dissociation, corectopia, occasionally oval pupil.
- Behavioral abnormalities: Somnolence, peduncular hallucinosis, memory difficulties, agitated delirium.
- Visual defects: Homonymous hemianopia, cortical blindness, Balint syndrome.
- Motor and sensory deficits.

Course. Indeed, the patient's MRI demonstrates restricted diffusion within the thalami bilaterally, consistent with acute ischemia (Fig. 6.1A). Circle of Willis 3D MIP angiography demonstrated complete occlusion of the distal basilar artery (Fig. 6.1B).

If the criteria for an intravenous or intra-arterial tissue plasminogen activator (tPA) are satisfied (see Case No. 2) and the deficit was less than three hours in duration, tPA treatment should be considered. Whether a tPA is given or not, the patient should be admitted for evaluation of the etiology of the top of the basilar syndrome and for treatment of stroke risk factors.

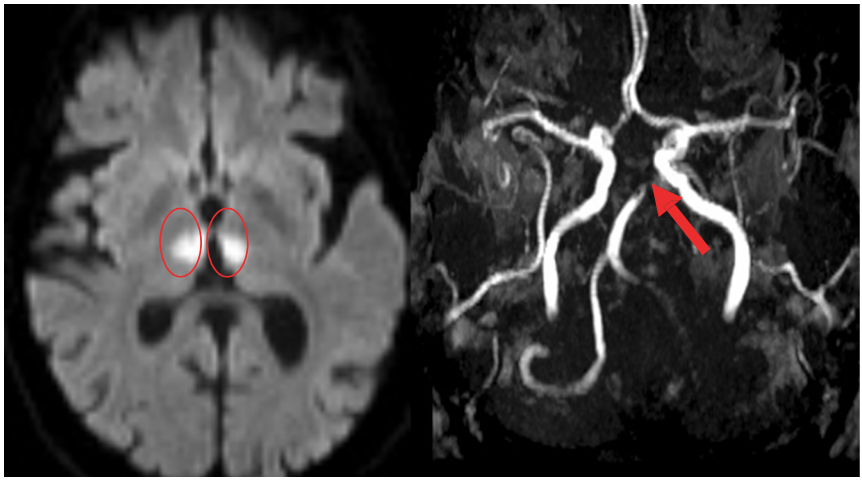

Fig. 6.1. Axial diffusion (left) demonstrates restricted diffusion within the bilateral thalami (circle) consistent with acute ischemia. Circle of Willis 3D MIP angiography (right) demonstrates complete occlusion of the distal basilar artery (arrow).

Dr. Lee. In the modern neuroimaging era, patients can undergo a CT and sometimes an MRI within hours of presentation. If the studies are performed this acutely, the structural imaging can be normal. A patient with an apparently unilateral and presumed "ischemic" third nerve palsy can have a normal CT and MRI. If bilateral ocular motor cranial neuropathy signs appear, then the differential diagnosis includes Bickerstaff's encephalitis, botulisum, Miller Fisher variant, myasthenia gravis, Wernicke syndrome and Whipple's disease. The normal neuroimaging may give rise to a false sense of security, however, if diffusion-weighted imaging (DWI) is not included in the study. The DWI might show a bright signal (i.e. restricted diffusion) bilaterally due to "top of the basilar" thrombosis producing acute ischemia at the mesencephalic-thalamic junction, even though the initial structural studies are normal.

Practice Essentials

— The differential diagnosis in cases of bilateral ophthalmoplegia include brainstem lesions and botulism, Myasthenia Gravis and Miller Fischer, Wernicke and Whipple, Cavernous sinus lesion, and carcinomatous

meningitis. These etiologies can be summarized using the mnemonic acronym "BMW CAR."

— The first step would be giving a thiamine shot, considering the low cost and safety profile, followed by neuroimaging. It is highly likely that the initial CT scan will be negative, so MR imaging is warranted, considering the above differential mostly appears on an MRI rather than a CT scan. Other investigations should be based on accompanying signs and disease course.

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CHAPTER · 7

Acute Unilateral Optic Neuropathy

CASE NO. 7

A 44-year-old white female presented in the Emergency Room (ER) complaining of gray vision in her left eye for three days. She also described some left eye pain that was worse with eye movement. She denied any other neurological symptoms. Past medical history was unremarkable.

On examination, her visual acuity was 20/20 OD and count fingers 6 feet OS. The pupillary examination showed 1.5 log unit afferent pupillary defect in the left eye. Ocular motility was full, but the patient noted some eye pain during movement. Slit lamp examination was unremarkable in each eye. Intraocular pressure was 16 mm Hg in each eye. Funduscopic examination showed a cup-to- disc ratio of 0.3 in each eye. The macula, vessels, and periphery were unremarkable.

Discussion

Dr. Brazis. The patient's clinical features are most consistent with optic neuritis (ON). ON is an inflammatory or autoimmune disease process affecting the optic nerve, causing relatively acute impaired vision, and progressing over hours or days. Visual function is typically worse by one week, and the disease process is predominantly unilateral. ON is more common in women (77%) and usually affects patients who are 20 to 50 years of age (mean age, 32 years). Pain, often

induced or exacerbated by eye movement, accompanies visual loss in greater than 90% of patients. The optic disc is normal in approximately two-third of patients (retrobulbar ON) and swollen in one-third. Color vision is often affected more than visual acuity. Visual function is especially decreased in the central 20° of the visual field, with various abnormalities noted on perimetry. In the majority of patients, vision improves in the second or third week and is often normal by the fourth or fifth week. However, some patients do not improve to a functional level or at all.

The clinical features of a typical ON include:

- Acute, usually unilateral loss of vision
  - Visual acuity (variable visual loss 20/20 to NLP [no light perception])
  - Visual field (variable optic nerve visual field defects)
- A relative afferent pupillary defect (RAPD) in unilateral or bilateral but asymmetric cases
- Periocular pain (90%), especially with eye movement
- Normal (65%) or swollen (35%) optic nerve head
- A young adult patient (<40 years), but ON may occur at any age
- Eventual visual improvement
  - Improvement over several weeks in most patients (90%) to normal or near normal visual acuity
  - 88% improve at least one Snellen line by day 15
  - 96% improve at least one line by day 30
  - Visual recovery may continue for months (up to 1 year)
- Patients may complain of residual deficits in contrast sensitivity, color vision, stereopsis, light-brightness, visual acuity, or visual field

Patients who meet these criteria are considered to have typical ON. Conversely, patients with the features listed below have atypical ON. Fundus features which should lead the examiner to consider an alternate diagnosis to ON include lipid maculopathy (“macular star”), very severe disc edema with marked hemorrhages, cotton wools spots, vitreous cells, pale optic disc edema, retinal

arteriolar narrowing, or retinopathy. Additional features suggesting an atypical ON for demyelination include:

- Bilateral simultaneous onset of ON in an adult patient
- Lack of pain
- Severe headache (e.g. sphenoid sinusitis)
- Ocular findings suggestive of an inflammatory process
    - Anterior uveitis
    - Posterior chamber inflammation more than trace
    - Macular exudate or star figure
    - Retinal infiltrate or retinal inflammation
- Severe disc swelling
- Marked hemorrhages
- Lack of significant improvement of visual function or worsening of visual function after 30 days
- Lack of at least one line of visual acuity improvement within the first three weeks after the onset of symptoms
- Age greater than 50 years
- Pre-existing diagnosis or evidence of other systemic condition
- Inflammatory (e.g. sarcoidosis, Wegener's granulomatosis, systemic lupus erythematosus)
- Infectious disease (e.g. Lyme disease, tuberculosis, human immunodeficiency virus infection)
- Severe hypertension, diabetes, or other systemic vasculopathy
- Exquisitely steroid sensitive or steroid dependent optic neuropathy

In atypical cases, consideration should be made for a lumbar puncture and additional laboratory studies. The required evaluation depends on the history and examination, with specific attention to infectious or inflammatory etiologies. In addition, patients with inflammatory autoimmune ON often have progressive or recurrent, steroid responsive, or steroid dependent optic neuropathy.

The Optic Neuritis Treatment Trial (ONTT) was developed to evaluate the efficacy of corticosteroid treatment for acute ON and to investigate the relationship between ON and multiple sclerosis (MS).

The ONTT was sponsored by the National Eye Institute as a randomized controlled clinical trial that enrolled 457 patients at 15 clinical centers in the United States between the years 1988 and 1991. The ONTT entry criteria included patients between ages of 18 and 46 years with a relative afferent pupillary defect as well as a visual field defect in the affected eye and examined within eight days of the onset of visual symptoms of a first attack of acute unilateral ON. Patients were excluded if they had previous episodes of ON in the affected eye, previous corticosteroid treatment for ON or MS, or systemic disease other than MS that might be a cause for the ON.

In the ONTT, all patients underwent testing for collagen vascular disease (antinuclear antibody [ANA]), serologic testing for syphilis (FTA-ABS), and a chest radiograph for sarcoidosis. Lumbar puncture was optional. An ANA antibody test was positive in a titer less than 1:320 in 13% of patients and 1:320 or greater in 3% of them. Only one patient was eventually diagnosed with a collagen vascular disease. Visual and neurologic outcomes in these patients were no different from those of the other ONTT patients. The FTA-ABS was positive in six patients (1.3%), but none had syphilis. A chest radiograph did not reveal sarcoidosis in any patient. However, in a separate report, other authors described a patient with isolated ON with a positive serology for Lyme disease. These authors recommended serologic testing for Lyme disease in patients with ON with or without the typical rash of erythema chronica migrans who live in or have visited Lyme endemic areas. Cerebrospinal fluid (CSF) analysis was recommended for patients with positive serology and intravenous (IV) antibiotic therapy for unexplained pleocytosis. We do not order Lyme titers for patients with ON from non-endemic regions.

The evaluation recommendations of the ONTT study group for patients with typical acute ON include:

Laboratory testing

Chest radiograph, laboratory tests (e.g. syphilis serology, collagen vasacular disease studies, serum chemistries, complete blood counts, etc.) and lumbar puncture are not necessary for typical ON but should be considered in atypical cases. (I also would consider Lyme serology in patients from endemic areas.)

Neuroimaging

Neuroimaging studies in the ONTT disclosed an alternative etiology for visual loss in only one patient with a pituitary adenoma; a second patient had an ophthalmic artery aneurysm that was not detected on the initial magnetic resonance (MR) scan. The ONTT authors concluded that neuroimaging was of limited value in establishing the diagnosis of ON. MR imaging of the brain was felt to be a powerful predictor of MS and should be considered to assess risk of future events of MS and for treatment decision-making.

ON is the presenting feature in 25% of patients with MS and occurs at some stage of the disease in 73%. In a study of 60 New England Caucasians with isolated ON, the risk of clinical MS developing in 15 years was 69% for women and 33% for men. In another study, life-table analysis showed that 39% of patients with isolated ON progress to clinically definite MS by 10 years of follow-up, 49% by 20 years, 54% by 30 years, and 60% by 40 years. This latter study did not note any difference in the risk of developing MS between men and women. In the ONTT, the 5-year cumulative probability of clinically definite MS was 30%. Brain MR scans performed at study entry was a strong predictor of the development of MS, with the 5-year risk of clinically definite MS ranging from 16% in 202 patients with no MR lesions to 51% in 89 patients with three or more MR lesions. The Optic Neuritis Study Group further studied 388 patients who experienced acute ON and followed up prospectively for the development of MS. The 10-year risk of MS was 38%.

Patients who had one or more typical lesions on the baseline MR imaging (MRI) scan of the brain had a 56% risk; those with no lesions (191) had a 22% risk. In a final 15-year follow-up report of the ONTT, 50% of the patients converted to definite MS. The risk of developing MS was 25% when the baseline MRI was normal and 75% when the MRI was abnormal (≥1 lesions). The risk of MS was significantly lower in males with a normal MRI and had optic nerve swelling and atypical features of ON. The eventual degree of disability was not related to the number of baseline MRI lesions.

In the ONTT, the patients were randomly assigned to one of three treatment arms in the study:

- IV methylprednisolone sodium succinate (250 mg every 6 hours for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days).
- Oral prednisone (1mg/kg daily for 14 days).
- Oral placebo for 14 days, followed by a short oral taper.

The major conclusions of the ONTT related to treatment are summarized as follows:

- High-dose IV steroids followed by oral corticosteroids accelerated visual recovery (particularly with visual field defects; $p = 0.0001$) but provided no long-term benefit to vision.
- "Standard dose" oral prednisone alone did not improve the visual outcome and was associated with an increased rate of new attacks of ON.
- IV followed by oral corticosteroids reduced the rate of development of clinically definite MS (CDMS) during the first two years, particularly in patients with MR signal abnormalities, but by three years, the treatment effect had subsided.
- MR findings were of prognostic significance for MS.
- Treatment was well tolerated with few major side effects (transient mood changes, sleep disturbances, dyspepsia, and weight gain, which occurred more commonly in the two steroid groups than in the placebo group. In the IV group, a psychotic depression developed in one patient and acute pancreatitis in another, both of which resolved without sequelae).

In a double-blind randomized trial, 383 patients who had a first acute demyelinating event (ON, incomplete transverse myelitis, a brainstem or cerebellar syndrome) were studied (CHAMPS study group). All had evidence of prior subclinical demyelination on MR imaging of the brain (two or more silent lesions of at least 3 mm in a diameter thought characteristic of MS). The patients received either weekly intramuscular injections of 30 μg of interferon beta-1a (193 patients) or a placebo (190 patients).

The patients had received initial treatment with corticosteroids. During three years of follow-up, the cumulative probability of the development of CDMS was significantly lower in the interferon beta-1a group than in the placebo group (rate ratio, 0.56). At three years, the cumulative probability was 35% in the interferon beta-1a group and 50% in the placebo group. As compared with the patients in the placebo group, patients in the interferon beta-1a group had a relative reduction in the volume of brain lesions, fewer new lesions or enlarging lesions, and fewer gadolinium-enhancing lesions at 18 months. The authors concluded that initiating treatment with interferon beta-1a at the time of the first demyelinating event is beneficial for patients with brain lesions on MR imaging that indicate high risk of CDMS.

The Early Treatment of Multiple Sclerosis (ETOMS) Study Group assessed the effect of interferon beta-1a on the occurrence of relapses in patients after the first presentation with neurological events, with these patients being at high risk of conversion to CDMS. Eligible patients had had a first episode of neurological dysfunction, suggesting MS within the previous three months and had strongly suggestive brain MRI findings. These patients were randomly assigned interferon beta-1a 22 μg or a placebo subcutaneously once weekly for two years. Neurological and clinical assessments were done every six months, and a brain MRI every 12 months. 241 (78%) of 308 randomized patients received the study treatment for two years; 278 (90%) remained in the study until termination. Fifty-seven (85%) of 67 who stopped the therapy did so after conversion to CDMS. Fewer patients developed CDMS in the interferon group than in the placebo group (52/154 [34%] versus 69/154 [45%]). The time at which 30% of patients had converted to CDMS was 569 days in the interferon group and 252 in the placebo group. The annual relapse rates were

0.33 and 0.43, respectively. The number of new T2-weighted MRI lesions and the increase in lesion burden were significantly lower with active treatment. The authors concluded that interferon beta-1a treatment at an early stage of MS had significant positive effects on clinical and MRI outcomes.

Course. Our patient underwent an MRI study of the brain and orbits. Orbit MRI axial T1 post contrast with fat suppression demonstrates the abnormal left optic nerve enhancement (Fig. 7.1). Brain MRI coronal FLAIR (fluid attenuation inversion recovery) imaging demonstrates an abnormal increased T2 signal in the right periventricular white matter consistent with demyelinating disease (Fig. 7.2).

Because the patient is thought to be at risk for the development of MS in the future, she was offered IV corticosteroids to decrease or delay the risk of subsequent attacks. She was sent to a neurologist specializing in MS to discuss the use of immunomodulating therapies to decrease her subsequent risk of MS attacks and perhaps delay the onset of clinical MS.

Fig. 7.1. Orbit MRI axial T1 post contrast with fat suppression demonstrates the abnormal left optic nerve enhancement (arrow).

Fig. 7.2. Brain MRI coronal FLAIR demonstrates an abnormal increased T2 signal in the right periventricular white matter (arrow) consistent with a demyelinating disease. Other similar white matter lesions were seen in the periventricular white matter on other images.

Dr. Lee. ON is a common cause of acute unilateral visual loss in a young patient. In patients with severe visual loss (e.g. 20/400 or worse), the clinician might make the mistake of skipping the formal visual field, especially with other evidence for an optic neuropathy (e.g. RAPD, visual field defect, normal or hyperemic disc). The temptation is to make the clinical diagnosis of ON and schedule an outpatient MRI study. My recommended optic neuropathy protocol is a head and orbit study with T1 fat suppressed orbital views with gadolinium to look at the optic nerve, T1 axial post contrast brain to look for enhancing white matter lesions of active disease, and sagittal, coronal, and axial T2-weighted FLAIR studies to look for demyelinating periventricular white matter lesions. If an imaging study is going to be deferred, the clinician should still test the fellow eye, even if asymptomatic, to look for evidence of not only optic neuropathy but also contralateral superotemporal visual field loss (i.e. the junctional scotoma) that might suggest an alternate diagnosis to ON such as a compressive lesion. Acutely pituitary apoplexy and ophthalmic artery aneurysm can both mimic a painful acute optic neuropathy, but the junctional

scotoma is definitely a red flag for a compressive rather than a demyelinating etiology. Likewise, patients who are elderly are unlikely to experience ON. The diagnosis of ON does occur in elderly patients, but I always recommend cranial and orbital optic nerve directed neuroimaging. A retrobulbar acute painful optic neuropathy in an elderly patient is more likely to be posterior ischemic optic neuropathy from giant cell arteritis or a compressive lesion, including orbital apex fungal disease rather than demyelinating ON. In addition, longitudinally extensive enhancement of the optic nerve, bilateral, or chiasmal involvement might suggest autoimmune, antibody mediated inflammatory ON (e.g., aquaporin-4 (AQ-4) antibody) like neuromyelitis optica (NMO) spectrum disease. Enhancement of the optic nerve sheath (perineuritis) or extension into the orbital fat might suggest myelin oligodendrocytic glycoprotein (MOG) mediated ON.

Currently, ON can be classified as:

- MS-associated
- Not MS
    - clinically isolated syndrome (CIS)
    - NMO or MOG
    - Other infectious or inflammatory (Sarcoid, systemic lupus erythematosus, GPA, syphilis, tuberculosis, Zoster), or congenital (i.e. Leber hereditary optic neuropathy [LHON]).

NMO and MOG have become separate entities since the discovery of their respective serum antibodies, with AQ-4 in NMO and MOG-Ab in MOG disease.

Any atypical feature in presentation (e.g. severe or bilateral), demographic (e.g. male or old), disease course (e.g. minimal to no response to steroid) should warrant investigation for alternatives, including NMO and MOG testing, rather than premature closure with isolated or MS. The importance of such a distinction is the difference in treatment after the first 3–5 days of 1 gm intravenous methylprednisolone (IVMP). They need lifelong treatment with slow steroid

tapering in MOG and maintenance in NMO rather than the quick 1-month tapering in MS or isolated ON.

Practice Essentials

— Typical ON present with moderate visual acuity loss in a patient with typical demographic for ON, including middle-aged Caucasian females. In the past, most patients with ON were treated as outpatients. However, any deviation from the above typical or suspicious neurological deficits (e.g. limb weakness) should warrant admission and further investigation for other differential, including neuromyelitis optica (NMO) and myelin oligodendrocyte associated disease (MOG).

— The recommended optic neuropathy protocol is a head and orbit study with T1 fat suppressed orbital views with gadolinium to look at the optic nerve, T1 axial post contrast brain to look for enhancing white matter lesions of active disease, and sagittal, coronal, and axial T2-weighted FLAIR studies to look for demyelinating periventricular white matter lesions.

— The treatment of choice is IV methylprednisolone for 3–5 days, followed by oral steroids. Plasma exchange and IV immunoglobulins should be considered if no vision improvement occurs with poor baseline vision. Avoid using oral steroids in patients with acute ON without prior IV steroid use, as this has been shown to increase the recurrence rate of ON.

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CHAPTER · 8A

Acute Pupil Spared Third Nerve Palsy

CASE NO. 8A

A 66-year-old white male presented in the Emergency Room (ER) complaining of a headache for the past few days. On that day, he noticed that his right eyelid was drooping. He noted double vision since awakening in the morning, so he decided to seek medical attention. His past medical history was remarkable for diabetes mellitus controlled with diet/exercise, hypertension controlled with furosemide (Lasix), and hypercholesterolemia controlled with statin therapy. His family history was unremarkable.

On examination, his visual acuity was 20/30 in each eye. Confrontation visual field was full in both eyes. Pupillary examination was normal without anisocoria or an afferent pupillary defect. Ocular motility was consistent with right third central nerve palsy (Figs. 8A.1 and 8A.2). Slit lamp examination showed a posterior chamber intraocular lens bilaterally and was otherwise unremarkable. Intraocular pressure (IOP) was 14 mm Hg in each eye. Funduscopic examination was within normal limits in both eyes.

Discussion

Dr. Brazis. We divide third nerve palsy (TNP) into non-isolated and isolated TNP. The isolated TNP were defined as TNP without associated neurologic findings (e.g. headache, other cranial neuropathies). Patients with evidence for

Fig. 8A.1. External photography showing partial right ptosis.

Fig. 8A.2. Ocular motility photography showing the right III nerve palsy.

myasthenia gravis (e.g. variability, fatigue, Cogan's lid twitch sign, enhancement of ptosis) are not included in the isolated TNP group. We define six types of TNP:

Type 1: Non-isolated

TNP is considered non-isolated in the presence of the following features:

- Orbital disease (e.g. chemosis, proptosis, lid swelling, injection, and positive forced ductions)

- Evidence to suggest myasthenia gravis (e.g. fatiguability of the motility defect, Cogan's lid twitch sign, orbicularis oculi weakness)
- Multiple cranial nerve palsies (including bilateral TNP) or radiculopathy
- Brainstem signs (e.g. hemiplegia, cerebellar signs, other cranial nerve deficits)
- Systemic, infectious, or inflammatory risk factors for TNP (e.g. history of previous malignancy, giant cell arteritis, collagen vacular disease)
- Severe headache

Type 2: Traumatic TNP

Isolated unilateral TNPs, which have a clearly established temporal relationship to significant previous head trauma and do not progress, are considered traumatic in origin. Patients with minor head trauma are not included.

Type 3: Congenital TNP

Patient born with an isolated TNP or noted to have a TNP within the first three months of life.

Type 4: Acquired, non-traumatic isolated TNP

- **Type 4A:** TNP with a normal pupillary sphincter with completely palsied extraocular muscles
- **Type 4B:** TNP with normal pupillary sphincter and incomplete palsied extraocular muscles
- **Type 4C:** TNP with subnormal pupillary sphincter dysfunction and partial or complete extraocular muscle palsies

Type 5: Progressive or unresolved TNP

Patients with TNP that worsen after the acute stage (greater than two weeks) or who develop new neurologic findings are considered to have progressive TNP. Patients without resolution of TNP after 12 to 16 weeks are considered unresolved.

Type 6: TNP with signs of aberrant regeneration

Non-isolated TNP should undergo neuroimaging, with attention to areas suggested topographically by the associated neurologic signs and symptoms.

Appropriate investigations and neuroimaging studies are directed at the precise area of interest, and this area determined by the associated localizing features with the TNP. In general, magnetic resonance (MR) imaging with and without gadolinium enhancement is the neuroimaging modality of choice for all these processes. Contrast-enhanced computerized tomography (CT) scanning with narrow (2 mm) collimation is reserved for those cases that cannot tolerate an MR scan or in whom an MR scan is contraindicated (e.g. pacemaker, claustrophobia, metallic clips in head, etc.). CT scanning is also the appropriate first choice neuroimaging study in patients being evaluated for acute head trauma or acute vascular events (infarction or hemorrhage). If there are clinical signs of a meningeal process, lumbar puncture (LP) should be performed.

The patient has an acquired, isolated, nontraumatic TNP. Acquired, nontraumatic isolated TNP may occur with lesions localized anywhere along the course of the third nerve from the fascicle to the orbit.

TNP with a normal pupillary sphincter and completely palsied extraocular muscles is almost never due to intracranial aneurysms. This type of TNP is most commonly caused by ischemia, especially associated with diabetes mellitus. Ischemic TNP may also occur with giant cell arteritis and systemic lupus erythematosus. Pupil-sparing TNP has also been reported with sildenafil citrate (Viagra) and similar agents and with cocaine use. Significant risk factors for ischemic oculomotor nerve palsies include diabetes, left ventricular hypertrophy, and elevated hematocrit. Obesity, hypertension, and smoking are also probable risk factors.

Ischemic lesions of the oculomotor nerve often spare the pupil because the lesion is confined to the core of the nerve and does not affect peripherally situated pupillomotor fibers. The pupil may, however, be involved in diabetic oculomotor palsies and diabetes may even cause a superior branch palsy of the oculomotor nerve. Pupil sparing has been documented in 62–86% of TNP due to ischemia. In a prospective study of 26 consecutive patients with diabetes-associated TNP, internal ophthalmoplegia occurred in 10 patients (38%). The size of anisocoria was 1 mm or less in most patients. Only two patients had anisocoria greater than 2.0 mm, and it was never greater than 2.5 mm. No

patient had a fully dilated, unreactive pupil. The author concluded that pupil involvement in patients with diabetes-associated TNP occurs more often than has previously been recognized (14%–32% in other studies), although the degree of anisocoria in any one patient is usually 1 mm or less. Patients who have oculomotor nerve palsies with anisocoria of greater than 2.0 mm are considered outliers for the diagnosis of ischemia.

In a prospective study of 16 patients with ischemic TNPs, 11 (69%) had progression of ophthalmoplegia with a median time between the reported onset and peak severity of ophthalmoplegia of 10 days. All patients with an ischemic TNP will improve within 4 to 12 weeks of the onset of symptoms.

Patients with an incomplete motor TNP with pupillary sparing require an MR scan to rule out a mass lesion. Pupil involvement is not diagnostic of aneurysmal compression, and up to 38% of presumed ischemic TNP involve the pupil.

Patients with a "relative pupil sparing" TNP should have MR imaging to rule out the possibility of a compressive lesion. Such patients should also have a CT scan if a subarachnoid hemorrhage (SAH) is suspected and a subsequent cerebral angiogram if an MR scan is negative because of the possibility of a cerebral aneurysm. In a small prospective study of 10 patients with "relative pupillary sparing" TNP, none of the patients demonstrated aneurysms. The authors suggested that the prevalence of aneurysm in patients with palsies of this type may be low enough to preclude routine angiography in the group. This report and the subsequent recommendation were, however, based on an inadequate patient sample. In another report of 24 patients with relative pupil-sparing TNP, the authors found that 10 had nerve infarction, eight had parasellar tumors, two had intracavernous carotid aneurysms, one had leptomenigeal carcinomatosis, one had Tolosa–Hunt syndrome, one had oculomotor neurilemmoma, and one had primary ocular neuromyotonia. Also, others have reported internal carotid, posterior communicating, and basilar artery aneurysms in isolated TNP with relative pupillary sparing. Thus, cerebral angiography may still be warranted if MR imaging is negative. Because up to 38% of patients with ischemic TNPs

have pupillary dysfunction, using these guidelines will yield a certain percentage of normal angiograms.

Complete external and internal TNPs occurring in isolation are often due to compressive lesions or meningeal infiltration. A fully dilated and non-reactive pupil occurs in up to 71% of patients with aneurysmal compression and TNP. Aneurysms impair the pupil in 96% of TNP and the remaining 4% in which the pupil is spared have only partial TNP.

After having reviewed the literature on MRI/MRA, CT and CT angiogram (CTA), and catheter angiography in the management of the isolated TNP, we proposed the following guidelines:

Isolated complete or partial internal dysfunction (pupil dilated) with completely normal external function of the third nerve and no ptosis

The risk for an aneurysm in this setting is minimal and neuroimaging for the aneurysm is probably not required. The clinician should look for other etiologies for isolated pupil dysfunction (e.g. tonic pupil, pharmacologic, sphincter damage).

Partial external dysfunction TNP without internal dysfunction

The risk for an aneurysm in patients with partial TNP is moderate (up to 30% of cases). Unfortunately, the risk for an individual patient is not well defined because other etiologies may cause a partial external dysfunction TNP with a normal pupil. For example, patients who have clear myasthenia gravis do not require additional aneurysm evaluation. Other non-aneurysmal etiologies, including neoplastic, demyelinating, infiltrative, and ischemic etiologies, may also cause a partial TNP without pupil involvement and may require neuroimaging. If the TNP is due to an aneurysm, the TNP usually progresses over time to a complete TNP with pupil involvement. Although there may not be internal dysfunction (pupil involvement) in a partial external dysfunction TNP, the term "pupil sparing" is probably not appropriate in this setting. That is, pupil involvement may occur over time in patients with partial TNP due

to an aneurysm with initially no internal dysfunction. Absence of pupil involvement early in the course of a partial TNP may be due to incomplete compression of the pupil fibers by the aneurysm. MRI with MRA or CTA in the acute setting is a reasonable screen in these cases. The patient should be followed clinically for progression or pupil-involvement in the first week. If the cranial MRI with MRA or CTA is negative and if the risk of angiography (e.g. elderly, severe cardiovascular disease, abnormal serum creatinine) is high, then observation alone is reasonable, and the clinician should look for alternative etiologies for a partial external dysfunction TNP (e.g. myasthenia gravis). The clinician should still consider catheter angiography in these cases if the risk of an aneurysm is higher than the risk of angiography (technically inadequate MRA, progression to complete TNP, pupil involvement). If a patient with a partial TNP has signs of meningeal irritation, other cranial nerve palsies, or signs of more diffuse meningeal involvement (e.g. radiculopathies), then a spinal tap to investigate infectious, inflammatory, or neo-plastic meningitis should be performed. In case of presumed or suspected SAH, a CT scan may be the preferred initial imaging study, followed by cerebral angiography.

Complete external dysfunction with completely normal internal function TNP

Although this clinical situation indicates a very low risk for an aneurysm and some authors argue that a vasculopathic patient may be observed for improvement, other authors recommend neuroimaging for TNP regardless of the completeness of the TNP or involvement or sparing of the pupil. In patients with initial pupil sparing, however, the pupil should be re-examined within the first week. Patients who develop pupil involvement should be evaluated using the recommendations outlined under pupil-involving TNP. Vasculopathic risk factors, especially diabetes mellitus, hypertension, and increased cholesterol, should be sought and controlled. Patients over the age of 55 years, especially those with other symptoms suggestive of giant cell arteritis (e.g. headache, jaw or tongue claudication, polymyalgia rheumatica symptoms), should have a sedimentation rate determination. Temporal artery biopsy should be performed if the sedimentation rate is elevated or other systemic symptoms are present.

If the patient has no vasculopathic risk factors, or if there is no improvement after 4–12 weeks, or if signs of aberrant regeneration develop, then a cranial MRI with MRA or CTA should be performed. Evaluation for myasthenia gravis should be considered in painless, non-proptotic, pupil-spared ophthalmoplegia, depending on the clinical situation.

Partial external dysfunction with partial internal dysfunction TNP

An initial cranial MRI with MRA (or CTA) is reasonable. If these studies are of excellent quality and negative, then the clinician should follow up on the patient for progression or complete internal dysfunction. The risk for an aneurysm in this setting, however (even with a negative MRI/MRA), is uncertain. Clinicians should still consider catheter angiography if the risk of an aneurysm in an individual patient is higher than the risk of angiography.

Complete external dysfunction with partial internal dysfunction TNP

The risk of an aneurysm for complete external dysfunction with partial internal dysfunction (partial pupil or "relative pupil sparing") is also unknown but probably lower than for partial external dysfunction with or without partial internal dysfunction. The risk for an aneurysm in this setting (even with a negative MRI/MRA or CTA) is uncertain. The clinician should consider catheter angiography if the risk of an aneurysm is deemed higher than the risk of angiography.

Isolated complete internal dysfunction with partial or complete external dysfunction TNP

This clinical situation has the highest risk for an aneurysm (86% to 100% of aneurysmal TNP have pupil involvement). An MRI with MRA or CTA of the head should be performed, but even with negative neuroimaging, there should be a strong consideration for catheter angiography.

Any patient with TNP and signs of subarachnoid hemorrhage

The presence of SAH (on an unenhanced CT scan or LP) essentially makes the issue of complete or incomplete TNP, as well as application of the "rule

of the pupil" moot. Unfortunately, most of the papers in the literature on aneurysms and TNPs have included non-neurologically isolated cases, including SAH. In general, an initial CT scan (with consideration for an LP) should be performed in patients with TNP and signs of SAH. The clinical picture of SAH (e.g. severe headache, meningismus, altered consciousness) can be mimicked by other intracranial etiologies such as pituitary apoplexy, and most clinicians would consider a CT scan as an initial neuroimaging study prior to consideration of an angiography. Patients with SAH on CT scan should probably undergo catheter angiography. Patients who cannot undergo a catheter angiogram (e.g. morbidly obese and unable to be placed on the angiography table) may have to undergo a cranial CT and CTA alone prior to intervention. In other cases of SAH, special MR imaging parameters, including FLAIR MRI and MRA, may be useful. Catheter angiography should be strongly considered even if the evaluations for SAH (e.g. CT, LP) are negative.

Patients who cannot undergo MRI or MRA

CT and CTA could be considered in selected cases, especially if MRA is not available or in cases where MR is contraindicated (e.g. obesity, claustrophobia, pacemaker). Although CTA has some advantages over MRA (especially if the location of the aneurysm is known), the superior quality of MRI has compared to CT in evaluating the entire course of the third nerve makes the combination of MRI/MRA superior to CT/CTA as the screening study for TNP. There is insufficient evidence to determine if a combination of MRI and CTA would be superior to MRI/MRA in patients with TNP.

Dr. Lee. The "rule of the pupil" is that an isolated pupil-involved TNP should be considered to be an aneurysm of the posterior communicating artery until proven otherwise. A corollary to the "rule of the pupil" has been that an isolated pupil-spared complete TNP in a vasculopathic patient is unlikely to be an aneurysm. The "footnote" to these rules, however, states that the rules should not be applied to patients with partial TNP. In the past, the risk of catheter angiography (and its attendant morbidity up to 1% and possible mortality up to 0.1%) had to be weighed against the risk of missing an aneurysm. Modern noncatheter-based angiography, including CTA and MRA, has made it easier

to proceed with less invasive and less risky imaging. A properly performed and interpreted CTA or MRA should detect 98% of aneurysms, producing a TNP. In my institution, CTA is our current initial procedure of choice, but because an MRI with contrast is a superior imaging study for non-aneurysmal causes of TNP, the combination of CTA and cranial contrast MRI is probably superior to either study alone. The remaining 2% of missed sensitivity includes the differences in technique, imaging quality, and the neuroradiologist's interpretation of the study. Thus, the experience of academic, tertiary referral center neuroradiologists spending extra time examining three-dimensional rotational images and source images from a non-catheter angiogram may not be replicable or generalizable to all situations. Unfortunately, there is no pathognomonic set of clinical findings that can exclude an aneurysm, and most patients with TNP will deserve consideration for some type of imaging study. I image TNPs which are nonisolated, progressive, are partial, have any involvement of the pupil, or show aberrant regeneration. I do not think that anyone would fault the clinician for imaging even an isolated, pupil-spared, complete TNP in a vasculopathic patient, but I generally at least offer observation for these cases, especially if the patient is already improving slightly by the time of my visit.

In my opinion, if the clinical suspicion for an aneurysm remains high after CTA/MRA, or if the non-catheter angiographic studies are insufficient to exclude an aneurysm, then consideration should still be given for catheter angiography in all TNPs, excluding perhaps the truly isolated, pupil-spared TNP in a vasculopath patient who improves over time.

Course. The patient underwent an outside MRI and MRA, which were reviewed and were negative. A decision was made not to perform a CTA. The pain resolved within two weeks and the ptosis and ophthalmoplegia all resolved after six weeks. The presumptive of an isolated ischemic TNP was made. The patient's internist optimized his blood pressure, blood sugar, and lipids.

CHAPTER · 8B

Acute Pupil Involved Third Nerve Palsy

CASE NO. 8B

A 52-year-old woman presented in the Emergency Room (ER) complaining of a sudden severe headache, followed by emesis and photophobia. While she was being driven to the ER, she felt her left eyelid starting to close.

In the ER, her visual acuity was 20/20 OD and 20/30 OS. The left pupil was dilated and unreactive to light. There was limitation in the adduction, elevation, and depression of the left eye and complete ptosis OS (Figs. 8B.1 and 8B.2). The remainder of the eye exam was normal.

Discussion

Dr. Lee. The clinical presentation of severe headache, nausea, vomiting, photophobia, and signs of a TNP should be considered to be a ruptured aneurysm until proven otherwise. Although a complete exam is important in all patients in this setting, getting to a diagnosis quickly and then performing an imaging study might be lifesaving. The motility findings are consistent with a TNP (Fig. 8B.2) and the pupil involvement should invoke the "rule of the pupil." The rule simply states that a pupil-involved TNP is an aneurysm of the posterior communicating artery-internal carotid artery junction until proven otherwise. Typically, in this setting, I would recommend starting with a

Fig. 8B.1. External photograph at presentation shows the complete left ptosis.

Fig. 8B.2. External photographs demonstrating a left third nerve palsy. Note normal abduction OS and there was intact intorsion on downgaze consistent with an intact fourth nerve function OS.

non-contrast CT of the head to exclude hemorrhage (e.g. parenchymal, intraventricular, or subarachnoid bleed) and a contrast CT angiogram for an aneurysm. If the non-contrast head CT shows subarachnoid hemorrhage or if the clinical exam is still highly suggestive of aneurysm, then catheter angiography might still be necessary, even with a negative CTA. The use of CTA alone in this setting is highly dependent upon the skill of the interpreting neuroradiologist and the quality of the institution's CTA technology and the individual CTA

images. In a patient with a TNP and no clinical or radiographic evidence for subarachnoid hemorrhage, then an MRI (MRA) is useful to exclude non-aneurysmal causes for TNP. Although in most centers, a CTA is superior to an MRA for the detection of an aneurysm. The MRI is superior to the CT scan for following the course of the third nerve for alternative etiologies other than an aneurysm. The order of testing: CTA followed by MRI (MRA), or vice versa, is an individual institution's decision, especially as both techniques (CTA and MRA) continue to improve and have proponents on both sides.

Dr. Brazis. Acute painful TNP is a neuro-ophthalmogic emergency requiring immediate CT and CTA. Immediate evaluation by a neurosurgeon or endovascular aneurysm specialist is required. I agree with Dr. Lee's comments about the use of CTA versus MRA.

Course. The non-contrast CT scan showed intraventricular hemorrhage (Fig. 8B.3). The CT angiogram showed a left posterior communicating artery aneurysm (PCOM) and another asymptomatic right MCA aneurysm (Figs. 8B.4A, 8B.4B, and 8B.4C). The patient underwent diagnostic and therapeutic catheter angiography with endovascular coiling and obliteration of the aneurysm via interventional radiology.

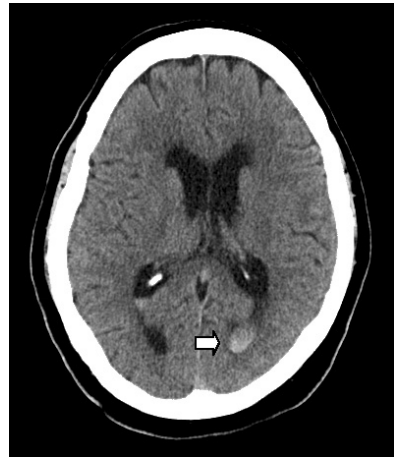

Fig. 8B.3. Non-contrast CT head shows hyperdensity consistent with blood in the ventricles (arrow).

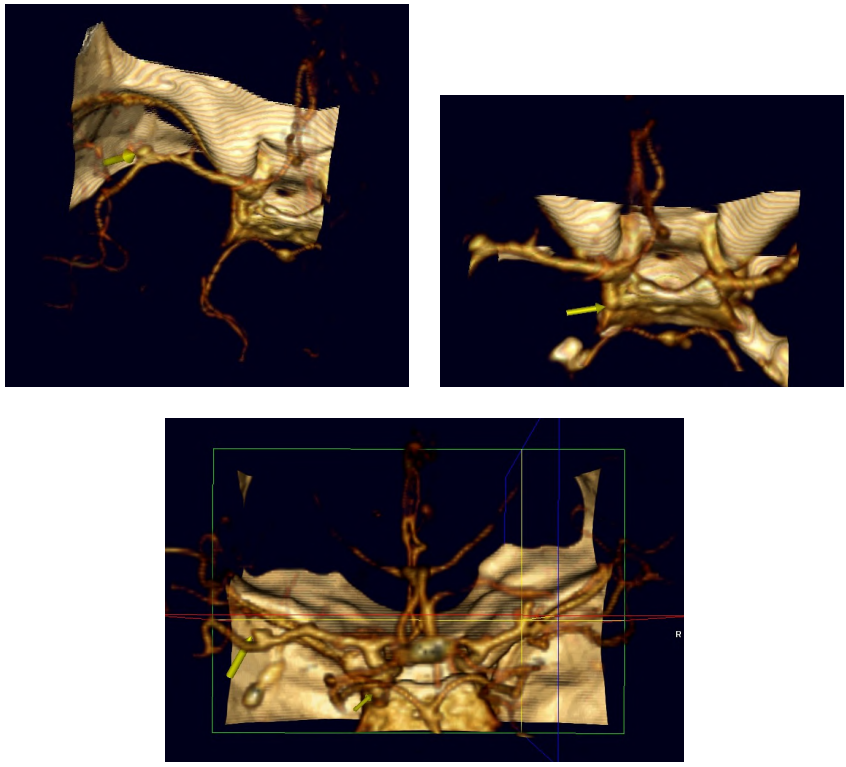

Fig. 8B.4. (A, B, C). A CT angiogram showing a left posterior communicating artery aneurysm (PCOM) on the upper left, right and bottom images, labeled with yellow arrow and a right MCA aneurysm.

She was discharged from the hospital two weeks later. The TNP improved slowly over the next four months but did not resolve completely (Figs. 8B.5 and 8B.6). A follow-up diagnostic CTA showed a complete obliteration of the aneurysm without recurrence. The second asymptomatic MCA aneurysm was treated one year later.

Practice Essentials

— Third cranial nerve (CN) is unique as it innervates most ocular muscles (except lateral recut and superior oblique) in addition to eyelid and pupillary muscles. However, the majority of oculomotor palsies are partial, manifesting with an incomplete picture of CN 3 palsy.

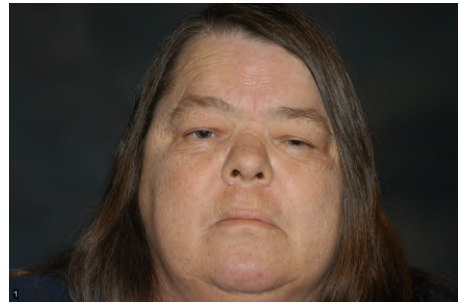

Fig. 8B.5. External photograph post endovascular coiling shows improving ptosis.

Fig. 8B.6. External photograph post coiling showing improved ophthalmoplegia.

— The most feared and relatively common etiology is posterior communicating artery aneurysm, and the clinical presentation of a severe headache with signs of TNP should be considered to be a ruptured aneurysm until proven otherwise.
— In cases with acute TNP, neuroimaging is warranted to exclude compression regardless of pupil involvement (i.e. the classic textbook pupil role), as this role was based on small retrospective studies, and more recent larger studies suggest the possibility despite pupil sparing. An other

important etiology that should be ruled out in the elderly is giant cell arteritis. Benign etiology with small vessel disease is most likely in isolated pupil-spared complete TNP in a vasculopathic patient.

— Neuroimaging should include MRI and MRA. CT and CTA could be considered in selected cases, especially if MRA is not available or in cases where MR is contraindicated.

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CHAPTER · 9

Acute Proptosis with Red Eyes

CASE NO. 9

A 55-year-old white female presented in the Emergency Room (ER) complaining that her eyes have been bulging, the right more than the left, for the previous few months. She also related constant pain in both eyes. She denied any decrease in her vision. However, she stated that her eyes were always inflamed. Her past medical history was remarkable for rheumatoid arthritis under control with a nonsteroidal anti-inflammatory. Her family was remarkable for heart disease.

On examination, her visual acuity was 20/25 in each eye. The confrontation visual field was normal in both eyes. Ocular motility showed mild restriction of adduction and abduction in both eyes. Pupillary examination was normal in both eyes without an afferent pupillary defect. Slit lamp examination showed conjunctival hyperemia and was otherwise unremarkable. Hertel measurement was 24 and 20 (Figs. 9.1 and 9.2). Ophthalmoscopy was within normal limits.

Discussion

Dr. Brazis. The clinical features most likely suggest Graves ophthalmopathy (GO). GO is characterized clinically by the following signs:

- Eyelid signs
  - Lid retraction (the most common clinical feature of GO)
  - Stare
  - Lid lag in downgaze

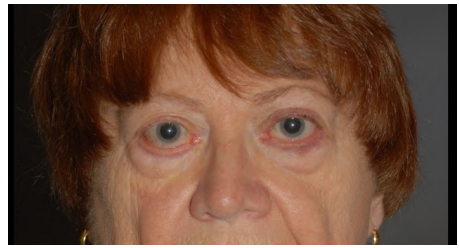

Fig. 9.1. External photography showing bilateral proptosis.

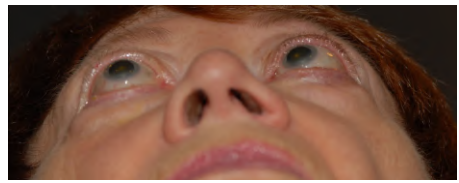

Fig. 9.2. External photography ("worm's eye view") showing proptosis OU.

- Exophthalmos
- Enlargement of extraocular muscles (EOMs)
- Increased orbital fat volume
- Increased intraocular pressure
- Diplopia/ophthalmoplegia secondary to extraocular muscle inflammation or fibrosis
- Visual loss
  - Exposure keratopathy
  - Compressive optic neuropathy (CON) from EOM involvement in the orbital apex
  - Stretching of the optic nerve due to proptosis
- Signs and symptoms of orbital congestion
  - Due to proptosis with or without venous outflow obstruction
  - Conjunctival injection and chemosis
  - Eyelid and periorbital edema
  - Tearing, photophobia, and orbital discomfort

Patients without the typical features of GO should undergo further evaluation for other etiologies of these signs: proptosis (e.g. orbital tumor or pseudotumor), strabismus (e.g. myasthenia gravis), and/or lid retraction.

The differential diagnosis for GO includes orbital inflammatory pseudotumor characterized by the following features:

- Typically unilateral but may be bilateral
- Clinical signs of orbital mass effect and inflammation (e.g. proptosis, chemosis, pain, injection, ophthalmoplegia)
- Neuroimaging shows focal or diffuse inflammatory lesion
- Histopathology reveals a fibro-inflammatory lesion
- No other identifiable local or systemic causes

With orbital pseudotumor, when the inflammatory process is confined to one or multiple EOMs, the process is referred to as orbital myositis, although some authors feel that orbital pseudotumor and orbital myositis may be distinct entities. Patients present with acute or subacute orbital pain and diplopia. Findings include conjunctival chemosis and injection, ptosis, and proptosis. Angle-closure glaucoma may rarely occur. The process may be unilateral or bilateral and usually resolves with corticosteroid therapy or radiation therapy. The illness is often monophasic but recurrent episodes may occur. Characteristics associated with recurrences include male gender, lack of proptosis, eyelid retraction, horizontal EOM involvement, multiple or bilateral EOM involvement, muscle tendon sparing on neuroimaging, and a lack of response to steroids or nonsteroidal anti-inflammatory agents. Orbital myositis may be associated with systemic diseases, such as Crohn disease, celiac disease, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), systemic lupus erythematosus, Whipple's disease, sarcoidosis, rheumatoid arthritis, linear scleroderma, and granulomatosis with polyangiitis (Wegener granulomatosis). Recurrent orbital myositis may occasionally be familial and orbital myositis may occasionally be paraneoplastic. Orbital myositis may rarely mimic cluster headaches and present with unilateral supraorbital pain, lacrimation, conjunctival hyperemia, nasal

congestion, proptosis, and painful eye movements. Inflammatory orbital pseudotumor may occasionally extend beyond the orbit.

Neuroimaging in orbital myosiits reveals enlarged, irregular muscles, usually with tendinous insertion involvement (as opposed to tendon sparing in GO). Intracranial extension of the inflammatory process is rare. The differential diagnosis of orbital pseudotumor is outlined below:

- Thyroid eye disease
- Orbital cellulitis (e.g. orbital apex syndrome) and infectious myositis
  - Bacterial
- Fungal
  - Aspergillosis
  - Mucormycosis
  - Bipolaris hawaiiensis
  - Actinomycosis
- Cysticercosis
- Trichinosis
- Gnathostomiasis
- Lyme disease
- Herpes zoster ophthalmicus
- Low flow dural-cavernous sinus fistula
- Immunoglobulin G 4 (IgG4 disease)
- Neoplastic
  - Metastatic
  - Breast cancer (false "orbital pseudotumor" presentation)
  - Lymphoid hyperplasia
  - Non-Hodgkin lymphoma and Hodgkin's disease
  - Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
  - Seminoma (bilateral nonspecific inflammatory or Graves-like orbitopathy not due to direct orbital metastasis)

- Infiltrative
  - Erdheim-Chester disease (idiopathic infiltration of the heart, lungs, retroperitoneum, bones, and other tissues by xanthomatous histiocytes and Touton giant cells).
  - Orbital amyloidosis
- Inflammatory
  - Sarcoidosis
  - Giant cell arteritis
  - Orbital polymyositis and giant cell myocarditis
  - Systemic inflammatory diseases (Wegener's granulomatosis, systemic lupus erythematosus)
  - Orbital inflammatory disease after pamidronate treatment for metastatic prostate cancer

With an orbital inflammatory pseudotumor, a biopsy may be required to exclude other diseases, except in pure myositic locations, in which the clinicopathologic picture is rather unique and surgical biopsy may damage the muscle, and in posterior locations, in which the optic nerve may be at risk during surgery.

Thyroid eye disease (thyroid orbitopathy, thyroid ophthalmopathy, or Graves disease) is a disorder characterized clinically by lid retraction, lid lag in downward gaze, exophthalmos, diplopia (due to EOM inflammation or fibrosis), potential visual loss due to CON or corneal damage, and signs and symptoms of orbital congestion. The restrictive EOM involvement may be confirmed by impaired ocular motility during the forced duction test. The EOMs predominantly affected include the inferior, medial, and superior rectus muscles, and as the process causes muscle tightness or restriction, the diplopia is worse in the direction opposite to that of the involved muscle(s) action. Thus, hypertropia and esotropia are quite common in thyroid eye disease, but exotropia is uncommon because the lateral rectus muscle is usually not markedly involved. In fact, if a patient with thyroid eye disease is noted to be exotropic,

superimposed myasthenia gravis should be considered as there is an increased risk of myasthenia gravis in patients with thyroid eye disease.

Thyroid eye disease and orbital myositis may resemble each other clinically. Differential features are outlined below:

Orbital Myositis	Thyroid Eye Disease
• Male = Female	Females predominate
• Acute or subacute onset	Gradual onset
• Often severe orbital pain	Painless or "foreign body" sensation
• Motility problems early	Motility problems late
• Limited (paretic) ductions	Restrictive ductions
• No lid lag or retraction	Lid lag and retraction
• Neuroimaging of orbit	Neuroimaging of orbit
o Enlarged muscles irregular	o Enlarged muscles often smooth
o Tendon spared	o Tendon may be involved
o Often unilateral	o Often bilateral

Orbital imaging, such as computed tomography (CT) and magnetic resonance (MR) scans, often demonstrate proptosis, EOM enlargement sparing the tendons, increased orbital fat volume, and sometimes engorgement of the superior ophthalmic vein. MR imaging may be superior to a CT scan in differentiating EOM edema (with elevated T2 relaxation times) from fibrosis. Serial short tau inversion recovery (STIR) sequence MR imaging findings may correlate with the clinical activity score. Ultrasonography of the orbit can also demonstrate EOM enlargement consistent with GO. MR imaging, however, is usually more costly than CT imaging.

Apical compression of the optic nerve in CON may be seen on CT or MR imaging. Coronal as well as axial images are useful in the radiographic diagnosis of CON in GO. We recommend orbital imaging in patients with clinical

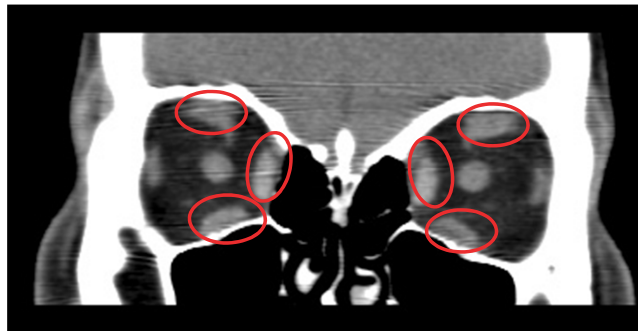

Fig. 9.3. Orbital coronal CT demonstrates the enlargement of the inferior rectus, superior rectus, and medium rectus bilaterally (circles).

evidence of an optic neuropathy and in cases where the diagnosis is uncertain or atypical features are present.

Course. The patient had a CT study of the brain and orbits. Orbital coronal CT demonstrates the enlargement of the inferior rectus, superior rectus, and medium rectus bilaterally (Fig. 9.3).

Treatment of the underlying systemic thyroid abnormalities is the logical first step in the management of thyroid disease. The evidence is controversial regarding the effect of the degree of thyroid abnormality or the speed, type (e.g. medical or surgical), or completeness of systemic therapy on the incidence or severity of GO. Nevertheless, we recommend that systemic thyroid control be achieved, and this may improve the signs and symptoms of GO. In a study of 90 patients with GO and hyperthyroidism in whom the severity of GO and thyroid function were assessed, patients were assigned to four groups with increasingly severe GO. More dysthyroid patients were in the groups with severe GO than in the other groups. Other uncontrolled studies, however, failed to show regression of GO after careful treatment of hyperthyroidism. Some authors believe that patients may experience worsening of GO after any systemic thyroid treatments (e.g. thyroid surgery, RAI (radioiodine therapy), and neck radiotherapy for non-thyroidal neoplasms). The presumed mechanism for worsening GO is a leakage of thyroid antigens and an increased level of circulating thyroid autoantibodies.

Several studies have shown that smoking is associated with worsening GO, and we recommend discontinuing tobacco in all of our patients with GO. Smoking influences the course of GO during treatment in a dose-dependent manner. The response to treatment is delayed and considerably poorer in smokers. Insulin-dependent diabetes mellitus is also a risk factor for GO, and optic neuropathy occurs much more frequently (33.3%) in patients with GO and diabetes (and seems to have a worse prognosis) than in a total group of patients with GO (3.9%).

The natural history of the GO is variable, and although most GO appears within a few months of the diagnosis of hyperthyroidism, it may have developed many months to years prior to the diagnosis or many months to years after the onset of the systemic diagnosis of thyroid abnormality. Some patients never show clinical or laboratory evidence for systemic thyroid abnormalities (euthyroid GO). In many patients, GO is a self-limited disease that may not require any therapy and the disease often stabilizes within one to three years. Therefore, treatment is usually directed at short-term control of the inflammatory component of the disease (usually within the first 6 to 36 months); acute intervention for vision-threatening proptosis or CON; and long-term reconstructive management of lid retraction, strabismus, and proptosis.

Medical and other conservative therapy should generally precede consideration of surgical intervention. A logical stepwise approach to the surgical rehabilitation of GO is proposed in the following four stages:

1. Orbital decompression
2. Strabismus surgery
3. Lid margin repositioning surgery
4. Blepharoplasty

The rationale for this sequential approach to GO is that orbital decompression often results in worsening, new, or changed EOM dysfunction, as well as changes in the lid position. Therefore, orbital decompression should, in general, precede strabismus and lid surgery in patients who require all three surgeries. Patients with CON should undergo treatment to preserve or improve vision.

A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for GO has been performed. The patients had symptomatic GO without optic neuropathy. Forty-two of 53 eligible consecutive patients were treated (20 Gy of external beam therapy to one orbit with sham therapy to the other side followed in six months with reversal of the therapies). Every three months for one year, the authors measured the volume of the EOM and fat, proptosis, range or EOM motion, area of diplopia fields, and lid fissure width. No clinical statistically significant difference between the treated and untreated orbit was observed in any of the outcome measures at six months. At 12 months, muscle volume and proptosis improved slightly more in the orbit that was treated first. The authors concluded that in this group of patients they were unable to demonstrate any beneficial therapeutic effects. The usefulness of this study has been criticized, however, because of its broad patient inclusion criteria that lack rigor in controlling the issues of timing of therapy, the clinical variability in presentation of the patients, and multiple treatment methods used for individual patients. The same authors performed a three-year follow-up of 42 of their patients who had received orbital radiotherapy within six months of the study entry. In this three-year uncontrolled follow-up phase, limited evidence for a clinically significant improvement was observed, which may have been the result of treatment or of natural remission. In either case, the changes were of little clinical significance. The authors concluded that because it is neither effective nor innocuous, radiotherapy does not seem to be indicated for treatment of mild to moderate ophthalmopathy.

The natural history of CON is poorly documented, but presumably, variable CON may be treated with systemic corticosteroids, orbital RT, or orbital surgical decompression. We recommend orbital decompression for proptosis in patients who have vision-threatening exposure keratopathy or other significant symptoms (e.g. pain, pressure, severe exophthalmos) related to the proptosis.

Dr. Lee. Thyroid eye disease is typically not a difficult clinical diagnosis. The most common cause of unilateral or bilateral proptosis in adults is thyroid eye disease. I generally make the diagnosis clinically based on lid retraction, lid lag, proptosis, and ophthalmoplegia. Ultrasonography or orbital non-contrast CT

scans is useful for confirming clinical findings but are not mandatory if there is no doubt about the diagnosis and there is no evidence for thyroid optic neuropathy. I recommend an assessment of both the activity and severity of disease. An active disease might benefit from immunosuppression versus inactive disease, which might benefit from reconstructive or rehabilitative surgical intervention. Severity drives the decision making for treatment. In my opinion, mild disease is best treated conservatively as the natural history is typically one of improvement, spontaneously, over time. CON, however, generally requires treatment, and it is reasonable to consider a short course of intravenous or oral steroids as a trial. Many patients have contraindications to steroids or may not be able to tolerate the side effects and so my threshold for surgical treatment is low. Orbital decompression may be necessary for vision-threatening CON. I recommend an orbital imaging study (generally a non-contrast CT scan) prior to orbital decompression and for patients who seem to have markedly asymmetric or strictly unilateral findings. Control of the systemic thyroid status and discontinuation of smoking are important first line treatments for all degrees of thyroid eye disease.

Practice Essentials

— Thyroid eye disease should be suspected in any patient with lid retraction, proptosis, or even conjunctival injection, even in the absence of underlying hyper- or hypothyroidism. It is thought to be immunologically mediated, where antibodies against thyroid attack the eye tissue.
— It has been suggested that thyroid eye disease has two phases: active inflammatory phase, where signs of inflammation can be observed and anti-inflammatory medications can help (e.g. steroids), and a non-inflammatory stable phase, where only consequences of the inflammatory phase are observed. It can also be staged into mild, moderate to severe, and dysthyroid optic neuropathy (DON), depending on the degree of manifestation.
— DON is a vision-threatening ophthalmic emergency and should be recognized in patients presenting with thyroid eye disease. While the diagnosis can be made clinically, orbital imaging can further demonstrate

enlarged orbital muscles with fatty infiltrations, which supports the diagnosis.

— Acute management for DON includes intravenous steroids for three days, followed by re-assessment in one week. Decompression surgery can be considered if worsening or no improvement in vision observed.

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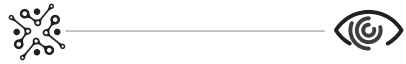
CHAPTER · 10



Acute Visual Loss in a Leukemia Patient

CASE NO. 10

A 5-year-old white female with a history of acute lymphoblastic leukemia presented in the Emergency Room (ER) for re-evaluation of new onset visual change and gait disturbance. She finished her chemotherapy four months previously and has been in remission. Her parents noticed a wider base gait over the past three days, and she started complaining of difficulty seeing early on the day she presented in the ER.

On examination, her visual acuity was 20/260 in each eye. Ocular motility was full. Pupillary examination was normal without an afferent papillary defect. Slit lamp examination was unremarkable in both eyes. Ophthalmoscopy showed grade IV optic nerve edema bilaterally.

Discussion

Dr. Brazis. Leukemias are usually classified according to the predominate cell type, the degree of differentiation within the cell line, and whether the process is acute or chronic. Acute leukemia occurs most commonly in the first five years of life, predominates in boys, and is most often lymphocytic. Chronic leukemias occur in older patients, with chronic myelocytic leukemia usually

developing in men 20 to 60 years of age and chronic lymphocytic leukemia affecting predominantly men between 45 and 60 years of age.

Neurologic complications of leukemia are caused by a variety of different processes. Neurologic injury may be caused by a leukemia invasion of the leptomeninges, parenchyma, spinal cord, nerve roots, and peripheral nerves. Leukemia may also cause cerebrovascular disorders, both hemorrhagic and ischemic, through obstruction of intracranial vessels. Neurologic sequelae may result from various forms of treatment of the disease. Some neurologic disorders in patients with leukemia are paraneoplastic. In most cases, however, leukemic involvement of the central nervous system (CNS) occurs from hematogenous spread or by direct invasion from the adjacent affected bone marrow.

CNS leukemia is diagnosed by cerebrospinal fluid (CSF) analysis, requiring a minimum typically of greater than 5 white cells/μL in the presence of leukemic blast cells, using cytospin techniques. Since the advent of successful therapy of leukemia, the meninges have become the major site of leukemic relapse. With the advent of intrathecal chemotherapy and cranial irradiation as a routine CNS prophylaxis, the incidence of meningeal leukemia has declined to approximately 10%. Leptomeningeal infiltration can lead to an infiltration of the intracranial portions of the optic nerve and chiasm. In most patients, visual loss may be slow and progressive, responding to radiation therapy, or extremely rapid.

Ocular findings are the initial manifestation in 3.6% of patients with acute childhood leukemia. Most ocular dysfunction in leukemia is related to a direct invasion by neoplastic cells; however, hematologic abnormalities associated with leukemia and the sequela of hyperviscosity also contribute significantly to visual morbidity. The main sites of involvement are the orbit and adnexal tissues, the retina, the optic nerve, and the uveal tract.

Sophisticated chemotherapeutic regimens and the use of prophylactic CNS irradiation in the treatment of leukemia have made the prognosis for long-term survival better. Survivors may suffer leukemic invasion of the optic nerve during a relapse and should be considered a potentially treatable cause of visual loss.

Clinical evidence of infiltration of the orbital portion of the optic nerve occurs primarily in children and adults with acute leukemia, especially those with the acute lymphocytic variety. Although active bone marrow disease and CNS involvement are usually present at the time the infiltration becomes evident, optic nerve infiltration may be the first manifestation of recurrence or relapse.

Leukemic infiltration of the optic nerve may produce two distinct clinical patterns. In one pattern, the prelaminar and laminar portion of the optic nerve are infiltrated; in the second pattern, the infiltration is retrolaminar. Infiltration of the optic disk occurs less frequently than does retrolaminar infiltration.

When the optic disk is infiltrated, the appearance is that of a fluffy, whitish infiltrate within the substance of the disk. The infiltrate is usually associated with disc swelling and hemorrhage. In this setting, the visual acuity is usually normal or only minimally reduced; however, if the infiltration, swelling, or hemorrhage extends to the macula, significant impairment of the central vision may occur. Leukemic infiltrates of the retrolaminar portion of the optic nerve is associated with a variable degree of optic disk swelling. The fluffy appearance that is characteristic of optic disk invasion is absent in such cases, but an associated retinopathy that includes evidence of both arterial and venous occlusion may be present. Leukemic infiltration of the retrolaminal portion of the optic nerve is usually associated with moderate to severe visual loss.

Because both patterns of leukemic infiltration of the optic nerve are associated with some degree of optic disk swelling, they must be differentiated from papilledema. In many cases, this is difficult, not only because in all three settings there is optic disk swelling associated with minimal, if any, visual loss but also because it is not unusual for optic nerve infiltration to occur simultaneously with meningeal infiltration and increased intracranial pressure. For this reason, in all patients who present with optic disk swelling in the setting of leukemia, neuroimaging studies and a lumbar puncture must be performed. CT scanning and MRI imaging typically show generalized enlargement of the affected optic nerve, often associated with a cuff of enhancement surrounding the nerve that represents leukemic cells.

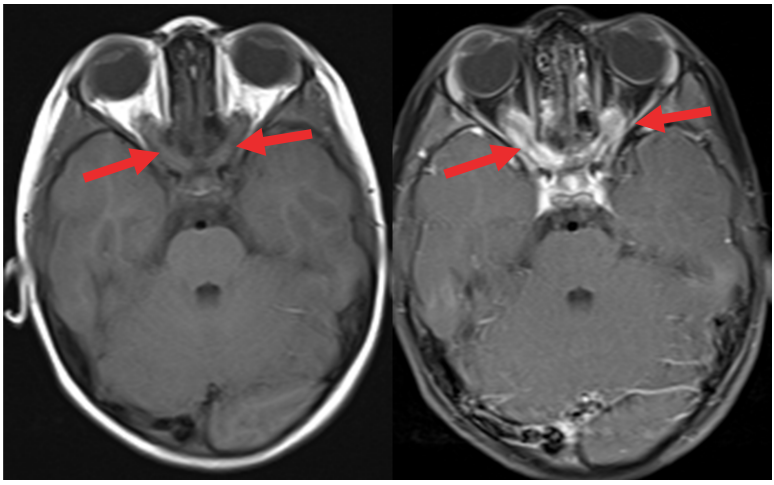


Fig. 10.1 (left): Brain MRI axial T1 without contrast demonstrates the enlargement of both optic nerves (arrows). (right): Brain MRI axial T1 post contrast with fat suppression demonstrates the abnormal enhancement of both optic nerves and chiasm (arrows).

Course. Brain MRI T1 images in our patient demonstrated enlargement of both optic nerves (Fig. 10.1, left). Brain MRI axial T1 post contrast imaging with fat suppression demonstrated abnormal enhancement of both optic nerves and chiasm (Fig. 10.1, right).

Treatment of leukemia includes the use of chemotherapy, immunotherapy, and radiation therapy. The optimum treatment for infiltration of the optic nerves is usually prompt irradiation. Patients who receive about 2000 centigray (cGy) to the posterior globe and orbit usually show a rapid resolution of the disk swelling and infiltration that may be accompanied by an improvement of vision. Our patient's optic disk swelling resolved after chemotherapy (Fig. 10.2).

Dr. Lee. In general, patients who present with any neuro-ophthalmic complaint and a history of cancer should be presumed to have a recurrence of that cancer until proven otherwise. This is especially true for infiltrative neoplasms like leukemia. Leukemia can produce neuro-ophthalmic manifestations from the

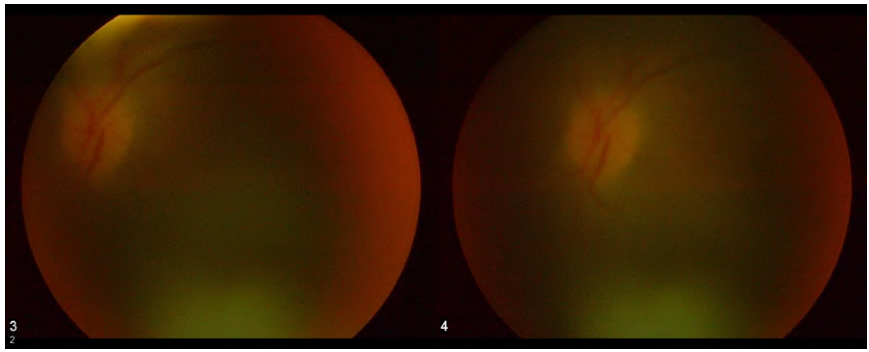


Fig. 10.2. Fundus photography showing the resolution of the optic nerve edema after chemotherapy.

leukemia per se, from the direct treatments for leukemia (e.g. radiation or chemotherapy), or from the side effects of treatment (e.g. immunosuppression, anemia, infection). Patients with an unexplained optic neuropathy who have underlying leukemia should generally undergo an aggressive evaluation (e.g. contrast enhanced cranial and orbital MRI with fat suppression and FLAIR sequences) to exclude CNS recurrence, and if negative, consideration for a systemic evaluation for leukemic relapse, and leukemic meningitis should be considered. The bottom line is that the clinician should be aware of a leukemia relapse in patients with any neuro-ophthalmic signs or symptoms.

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CHAPTER · 11

Acute Ophthalmoplegia After Vomiting

CASE NO. 11

A 20-year-old woman presents in the Emergency Room (ER) with a recent onset of blurred vision and diplopia. Her family has noted some confusion and mental status changes in her recently. She was one week post-partum and had suffered from hyperemesis gravidarum with persistent and recurrent vomiting, requiring intravenous fluids. Past medical history is significant for migraine and bipolar disorder. She admits to binge drinking alcohol 3–4 times a month but does not smoke cigarettes. She was not taking medications, however.

On examination in the ER, her visual acuity was 20/60 in each eye. She had mild light-near dissociation of both pupils with no anisocoria. In the primary position she had upbeat nystagmus, which increased on upgaze, and the amplitude and frequency of the nystagmus diminished on downgaze. There was superimposed horizontal jerk nystagmus in the right and left gaze (Fig. 11.1). There was a small angle esotropia noted in the primary position and she had mild but symmetric upgaze restriction OU. The remainder of the eye exam was normal. A CT scan of the head in the ER was normal.

Fig. 11.1. In the primary position, she had a small angel esotropia, and a slightly diminished upgaze bilaterally was noted. Not shown in this static photo is the upbeat nystagmus, which increased on upgaze and diminished on downgaze with no null point. There was superimposed horizontal jerk nystagmus in the right and left gaze.

Discussion

Dr. Lee. A patient with acute onset of mental status changes, nystagmus, and diplopia in the ER and a negative cranial imaging for a posterior fossa lesion should be evaluated for Wernicke encephalopathy (WE). Although classically Wernicke syndrome is associated with alcohol abuse, there may be an inaccurate or unknown or admitted prior history of alcohol use. The increasing use of bariatric surgery in the United States has increased the number of non-alcohol related cases of Wernicke that I have seen in my practice. In addition, malnutrition, use of total parenteral nutrition, and persistent vomiting (e.g. hyperemesis gravida) can produce the Wernicke syndrome. The triad includes ataxia, ophthalmoplegia or nystagmus, and mental status changes, and may occur with any or all of the above. I would perform an MRI with contrast, but regardless of the imaging, I tend to recommend giving empiric thiamine and magnesium to patients in the ER with acute unexplained ophthalmoplegia or acute nystagmus, as the downside is minimal. I tend not to order the thiamine level and just treat empirically. In patients with unexplained ophthalmoplegia

or nystagmus, imaging might show a brainstem lesion (e.g. neoplastic, infiltrative, traumatic, vascular, ischemic, demyelinating).

Dr. Brazis. In this patient, my major concern would be WE. This is an organic global confusional ataxic condition usually thought of as seen in alcoholics and caused by thiamine deficiency. Patients with anorexia, severe weight loss of any cause, persistent vomiting, starvation of any cause, and who are desperately ill in intensive care settings are all at risk for development of WE. Stupor and coma are rarely seen in the initial phase of WE, but untreated, WE will progress to stupor, coma, and death in a matter of days. The classic clinical triad of WE included ataxia, confusion, and ophthalmoplegia. A newer operational definition of the syndrome emphasizes nutritional deficiency as the primary feature. Despite the importance placed on the ocular motor findings in both the classic and revised criteria for diagnosis, the incidence of these clinical findings is relatively low, occurring in only about a quarter to a third of the patients studied at necropsy.

The visual problems seen with WE include bilateral, frequently asymmetric ocular motility disturbances, and rarely acute nutritional optic neuropathy. Eye movement abnormalities include horizontal disturbances (e.g. gaze palsy, abduction paresis, vestibular paresis, internuclear ophthalmoplegia, horizontal nystagmus) and vertical disturbances (e.g. gaze evoked upbeat and/or downbeat nystagmus and skew deviation). Asymmetry of the pupil size and impaired light response have also been reported in 19% of patients with WE, but this is the same incidence as simple anisocoria, which occurs in 19% of the population at any given time.

The cause of WE is a deficiency of vitamin B1 (thiamine), which is a key coenzyme at three different points in intermediate carbohydrate metabolism. Depletion of thiamine and the subsequent stress of a glucose load may result in the relatively abrupt onset of WE. Blood levels of thiamine may be normal even in deficiency states, but blood transketolase levels reflect low thiamine levels more accurately. In this patient, however, we should not await the results of blood tests to initiate treatment. In addition, one should obtain serum magnesium levels (magnesium is a cofactor in glycolysis, which utilizes thiamine). If magnesium is low, it should be replaced when patients with WE

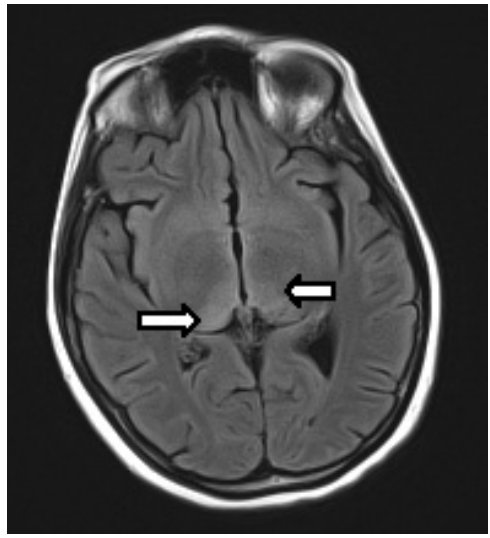

Fig. 11.2. Axial FLAIR sequence shows hyperintensity of the bilateral medial thalami (labeled with arrow).

are treated. Thiamine given in a patient with WE, when the magnesium level is low, will fail to reverse the clinical features of WE.

As far as neuroimaging in a patient is concerned, CT studies are of no help. MRI in patients with WE reveals a number of lesions best seen on FLAIR, T-2, and diffusion-weighted imaging (DWI) sequences. High signals are found in medial thalamus, the hypothalamus, the mamillary bodies, in the peri-aqueductal region, and surrounding the fourth ventricle. Other areas include the basal ganglia, cerebral cortex, pons, and medulla. Imaging after treatment frequently shows generalized atrophy and volume loss throughout the entire brain.

The patient should receive the immediate administration of IV Thiamine up to 500 mg three times a day (TID) and magnesium sulphate ($MgSO_4$) (especially if serum Mg levels are low). Oral thiamine, 50 mg daily, should be administered thereafter.

Course. MRI showed high signal intensity in bilateral thalami (Fig. 11.2). The patient was treated with empiric thiamine and magnesium and her nystagmus

and diplopia resolved. The mental status improved and the patient was subsequently discharged.

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CHAPTER · 12

Acute Anisocoria

CASE NO. 12

A 25-year-old female reports a difference in the size of her pupils after returning from a Caribbean cruise. The pupil was largest during the previous two days but appeared to have become slightly smaller. She denied any headache, ptosis, or diplopia and she had no other general or neurologic symptoms. She states that the left pupil is larger than her right pupil and that this was not present previously. Her past medical, surgical, family, and social history are non-contributory. The patient is a nurse and is concerned about having an "aneurysm."

On exam, her visual acuity was 20/20 OU. The right pupil measured 4 mm and was normally reactive to light. The left pupil measured 6.5 mm and was sluggishly reactive to light (Fig. 12.1). There was no light-near dissociation of the pupils. Both pupils were round. The slit lamp examination was normal OU. The intraocular pressure was normal OU. The motility exam was full and the eyes were straight in the primary position and the diagnostic positions of gaze. There was no ptosis. The fundus exam was normal OU.

Discussion

Dr. Lee. The evaluation of anisocoria is relatively straightforward and requires an assessment of the pupil light reaction and a measurement of the anisocoria

Fig. 12.1. External photography showing the left pupil is larger than the right pupil (anisocoria).

in the light and in the dark. In general, if the problem is strictly unilateral, then if the pupil reaction is impaired in one pupil, then that pupil is the problematic eye. If the pupil reaction to light is normal in each eye, then assessing the anisocoria in the light and in the dark helps to establish if the small pupil is not dilating (e.g. Horner syndrome) or if the larger pupil is not constricting properly. In this case, the left pupil is sluggishly reactive to light, indicating a problem with the efferent parasympathetic pupillary pathway or the iris on this side. If confronted with an abnormality in any one of the following three areas of the exam, namely the lid, pupil, or motility, then the clinician must always check to ensure a normal exam in the other two exam areas (I like to refer to this as "Savino's rule"). In this case of anisocoria with a larger pupil that is poorly reactive to light, the main concern is to exclude a third cranial nerve palsy. A careful assessment of the lid to exclude ptosis and an orthoptic evaluation in the primary and in the diagnostic positions of gaze is critical to ensure that the pupil finding is isolated.

An isolated dilated and poorly reactive pupil may be due to pharmacologic dilation, Adie tonic pupil, or local iris damage. The slit lamp examination is typically sufficient to eliminate local iris trauma or iris sphincter tear, or anterior segment inflammation. Assessment for increased intraocular pressure (IOP) is useful as an elevated IOP can lead to damage to the iris muscle due to ischemia.

In patients with a fixed and dilated larger pupil and no other evidence for a third nerve palsy (TNP), topical testing with pilocarpine 1% might be useful to demonstrate that the pupil is pharmacologically blocked. Once the pharmacologic block starts to wear off, the diagnosis can be more difficult, but the main concern is to exclude a TNP. If the patient has benign episodic pupillary dilation rather than pharmacologic blockade, it probably makes no difference in the end.

Dr. Brazis. As noted by Dr. Lee, patients with anisocoria and a poorly reactive pupil should be evaluated for an ipsilateral TNP.

A young patient with a thunderclap headache and a dilated pupil on one side has an aneurysm until proven otherwise. Check the ocular motility and lid for other signs of third nerve paresis. The pupil sign can be the first clue to an impending TNP and subarachnoid hemorrhage. Although an extra-axial lesion (e.g. unruptured intracranial aneurysm) compressing the third nerve may cause a dilated pupil in isolation (or with minimal ocular motor nerve paresis), in the absence of an extraocular motility deficit and/or ptosis, an isolated dilated pupil is usually not due to third nerve paresis. If there are signs of motility impairment suggesting a TNP, emergency neurologic evaluation and investigations in the patient is necessary.

Look at the pupil both grossly with a penlight and with a slit lamp, looking for a response to light, the near stimulus, and see if there is evidence of sector weakness, particularly in the more dilated pupil, as this could be a tonic (Adie) pupil. With a tonic pupil, there is usually mydriasis with a poor or absent reaction to light but a slow constriction to prolonged near effort (light-near dissociation). Redilation after constriction to near stimuli is slow and tonic. Segmental vermiform movements of the iris borders may be evident on a slit lamp exam (due to sector palsy of other areas of the iris sphincter), and cholinergic supersensitivity of the denervated iris sphincter (constriction when 0.1% pilocarpine is instilled) may be demonstrated. Tonic pupils occur due to local damage to the ciliary ganglion or short ciliary nerves, as part of a widespread peripheral or autonomic neuropathy, or in otherwise healthy individuals (Adie tonic pupil syndrome). With time, ciliary muscle dysfunction tends to resolve, and the pupil becomes progressively miotic ("little old Adie's"). Some patients may have primary miotic Adie pupils without going through a mydriatic phase. There is a tendency for patients with unilateral Adie's syndrome to develop a tonic pupil in the opposite eye.

Damage to the iris due to ischemia, trauma, or an inflammatory process may cause mydriasis. The clinical characteristics suggesting abnormalities of

the iris structure as a cause for mydriasis include: no associated ptosis or ocular motility disturbance (vs. TNP), the pupil being frequently irregular with tears in the pupillary margin due to tears in the iris sphincter (vs. a smooth margin in drug-related pupillary abnormalities), irregular contraction of the pupil to light, the possible eventual development of iris atrophy, and poor or no response of the pupil to 1% pilocarpine.

Mydriasis may be induced by the instillation of a parasympathicolytic drug (e.g. atropine, scopolamine). For example, someone working with drugs like atropine or norepinephrine may get a little on the finger, and subsequently rub the eye. Or the mom who is demonstrating to her little child how easy it is to take an eye drop (atropine) may have inadvertently contaminated her fingers and transferred it to her own eye. Unilateral mydriasis may follow the use of transdermal scopolamine to prevent motion sickness, the accidental instillation into the eye of fluids from certain plants (e.g. jimsonweed) that contain belladonna and atropine-like alkaloids, and exposure to certain cosmetics and perfumes. A careful history is usually all that is required in patients with inadvertent or intentional (e.g. glaucoma medication, treatment with topical cycloplegics for uveitis) exposure to agents that may affect the pupil size.

Nurses, physicians, and other healthcare workers are particularly prone to inadvertent or intentional exposure to pharmacological mydriatics. The pupil size of patients with pharmacologic sphincter blockade is often quite large (>8 mm), often on the order of 10 to 12 mm in diameter, which is much greater than the mydriasis usually seen in a typical TNP or tonic pupil syndromes. The pupils are evenly affected 360° (vs. a tonic pupil) and smoothly affected around without irregularity (vs. iris trauma). A solution of pilocarpine (1%) causes constriction in the case of a third nerve lesion but does not modify the pupil size if the anisocoria is due to an atropinic drug or to iris damage. Remember, however, that some patients with the Adie syndrome of recent onset may have a fixed dilated pupil that fails to constrict to even a strong solution of pilocarpine. Adrenergic pharmacologic mydriasis (e.g. phenylephrine) may be clinically distinguished by blanched conjunctival vessels, residual light reaction, and a retracted upper lid due to sympathetic stimulation of the upper

lid retractor muscle. With adrenergic mydriasis, the pupil may react to bright light due to the working iris sphincter muscle, which can overcome dilator spasm.

Course. The patient's pupil returned to normal after one day. She later recalled using a scopolamine patch for motion sickness on the cruise ship.

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CHAPTER · 13

Optic Disc Edema with a Macular Star Figure

CASE NO. 13

An 11-year-old boy presents with acute unilateral loss of vision OD. He had recently received a new kitten as a gift from his grandmother, and he had been playing with the cat over the previous two weeks and received a few scratches. The past medical, surgical, family, and social history are unremarkable. He had mild flu-like symptoms one week prior to the visual loss but had no headache, lethargy, fever, lymphadenopathy or other neurologic symptoms or signs. The left eye was asymptomatic.

On exam, the patient's visual acuity was 20/200 OD and 20/20 OS. The pupils were 5 mm OU and both pupils were reactive to light, but there was a right relative afferent pupillary defect. Goldmann visual field testing showed a dense central scotoma OD but was normal OS. Slit lamp biomicroscopy, motility, and intraocular pressure measurements were normal OU. The fundus exam was normal OS. The patient was seen by an outside eye doctor who noted optic disc edema OD and made the diagnosis of "optic neuritis" and told the patient's family that the boy might have "multiple sclerosis." A cranial MRI was performed and was normal. The patient was seen three weeks later in the eye clinic and had the fundus findings shown in Fig. 13.1.

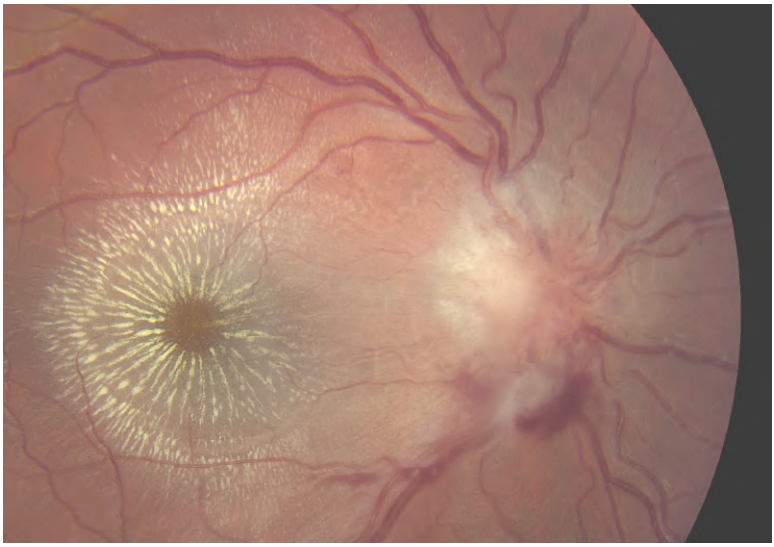

Fig. 13.1. Right eye fundus photograph shows marked disc edema, inferior peripapillary hemorrhage, and a full blown macular star figure.

Discussion

Dr. Bravis. Optic disc edema with a macular star (ODEMS) is a descriptive term encompassing a heterogeneous group of disorders. The condition has subsequently been called idiopathic Leber stellate maculopathy, Leber's idiopathic stellate neuroretinitis, or simply neuroretinitis. This syndrome is characterized by swelling of the optic disc, peripapillary and macular hard exudates, which often occur in a star pattern, and, often, vitreous cells. Because the macular exudate likely results from primary optic nerve disease and not a true retinitis, we prefer the term idiopathic ODEMS for idiopathic cases and use the term neuroretinitis when the optic disc swelling and a macular star are associated with retinitis, especially if an infectious cause is documented.

Patients are usually children or young adults, with the average age of onset of 20 to 40 years. Men and women are affected equally. Most cases are unilateral, but bilateral involvement has been noted to occur in up to a third of the cases.

Most patients present with acute unilateral loss of vision. The condition is often painless, but retrobulbar pain, pain on eye movement, or associated headache may occur. A nonspecific "viral" illness precedes or accompanies the visual loss in approximately half of the cases.

The clinical characteristics of ODEMS include:

- Age at onset: Childhood to young adult (6–50 years)
- Gender: Men = women
- Bilateral involvement: 5%–33%
- Pain: Occasional
- Antecedent viral illness: Approximately 50%
- Initial visual acuity: Variable (20/20 — light perception)
- Dyschromatopsia: Often prominent
- Visual field testing: Central, cecocentral, arcuate, or altitudinal defects; possible generalized constriction
- Relative afferent pupil defect present; but may be absent if bilateral involvement
- Optic disc swelling present with subsequent optic atrophy
- Macular star present but may take 1–2 weeks to develop
- Vitreous cells common (90%)

Optic disc edema is the earliest sign of ODEMS and may be severe. The disc edema tends to resolve over two weeks to two months, but in some patients, optic atrophy ensues. Optic disc edema is associated with the leakage of disc capillaries, with the fluid spreading from the disc through the outer plexiform layer of the retina. The serous component of the fluid accumulation in Henle's layer is reabsorbed, and the lipid precipitate forms a macular star. The macular star may be present at the onset of visual loss or may only be noted after one to two weeks following development of the disc edema. The macular star may even be observed only after the disc swelling has started to resolve. Patients with acute disc swelling with a normal macula should thus be re-examined within two weeks to investigate for the presence of a macular star, especially as it is of prognostic importance for the patient's subsequent risk of developing multiple sclerosis. Fluorescein angiography typically shows leakage from the

optic disc in the mid- to late phases with abnormal permeability of the deep capillaries in the optic nerve head but no perifoveal leakage.

Most cases of ODEMS are "idiopathic" and thought to be the result of a nonspecific viral infection or some immune-mediated process.

In general, ODEMS is usually a benign, self-limited inflammatory process. However, a number of infectious agents and inflammatory diseases have been reported to cause ODEMS and neuroretinitis. It appears that syphilis, cat scratch disease, Lyme disease, and perhaps toxoplasmosis are the most common causes of ODEMS and neuroretinitis in cases where an etiologic agent can be identified. Infectious agents should be aggressively sought in cases of ODEMS and neuroretinitis because appropriate antibiotic treatment might be indicated. We recommended special emphasis on recent patient travel history (Lyme endemic areas), consumption of unpasteurized or uncooked foods (toxoplasmosis), sexually transmitted disease exposure (syphilis), and animal contacts (cat scratch).

There is no proven treatment for idiopathic ODEMS. Steroids have been used in some cases with unclear effect. If a specific infectious agent is discovered, than appropriate antibiotics should be considered. However, the data is limited.

Dr. Lee. I agree with Dr. Brazis that the term "neuroretinitis" should be reserved for infectious causes of ODEMS to avoid confusion. The main emergency considerations for ODEMS are to exclude the mimics of infectious neuroretinitis. Patients with bilateral optic disc edema with a macular star figure might not have infectious neuroretinitis and instead might have disc edema from malignant hypertension or papilledema. I personally recommend considering imaging for bilateral cases, especially if there is no vitreous cell seen or if the history is not compatible with an infectious exposure. Although cat scratch neuroretinitis is the most common etiology in my experience for the presentation of unilateral optic disc edema with a macular star figure, it is not clear from the evidence that treatment makes any difference in outcome. Nevertheless, I generally treat patients with serologic confirmation of Bartonella related neuroretinitis.

Course. Bartonella henselae IgM titers were positive and acute and convalescent IgG titers showed a titer elevation at 1:2048. The patient was treated with oral antibiotics and two months later had complete resolution of the optic disc edema and resolution of the macular star figure of exudate. The vision improved to 20/30 OD, but there was residual retinal pigment epithelial atrophy in the macula OD.

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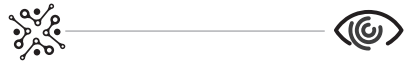
CHAPTER · 14



Acute Transient Monocular Visual Loss

CASE NO. 14

A 44-year-old female judge presented with several episodes of transient monocular visual loss in the right eye. She described the event as occurring rapidly over seconds, lasting 10 minutes, and rising like a curtain over her vision. There was no precipitating or palliating factor and the events spontaneously arose and abated. The patient had no history of hypertension or diabetes, but she was a heavy smoker (100 pack year history). She had no other neurologic signs or symptoms. She had a prior history of migraine headache in her twenties but no migraine visual aura. She saw an outside eye doctor and had a completely normal eye exam. She had no visual or other neurologic complaints at that visit. She denied any headache or pain. A diagnosis of "retinal migraine" was made, and the patient was sent home.

The following day, she developed several more episodes of amaurosis fugax OD. The patient called the eye doctor and was told to make an appointment with a neurologist for "migraine."

Discussion

Dr. Lee. Transient monocular visual loss lasting minutes in an altitudinal (i.e. curtain over my vision) fashion should be considered to be ischemic until

proven otherwise. The clinical dilemma is that although most cases of transient vision loss are benign (e.g. dry eye, corneal tear film disturbances), some cases are due to a potentially life-threatening cardioembolic source or visual-threatening giant cell arteritis (GCA).

The history and exam provide key clues that should drive the triage and decision making for emergent versus routine evaluation and follow up. Isolated transient visual loss (TVL) is a different management issue from that of neurologically non-isolated TVL. Patients who have associated transient or residual hemispheric signs (hemisensory loss, hemiparesis, or aphasia) should be evaluated for stroke, and consultation with our stroke neurology colleagues is advised. Likewise, if there is an acute and visible residual embolic event in the eye (e.g. branch or central retinal artery occlusion, Hollenhorst plaque), then I would defer to our stroke neurology colleagues for consideration for inpatient versus outpatient evaluation of cardioembolic sources (e.g. cardiac echo, carotid Doppler, laboratory studies).

The diagnosis of "retinal or ocular migraine" should be considered to be one of exclusion especially on the first event (which technically would not qualify for diagnosis by criteria). Many authors believe that this type of TVL is retinal vasospasm rather than migraine per se, but this remains controversial. In this particular patient, however, the dangerous red flags suggesting an ischemic origin to the TVL include the duration of minutes, the onset in seconds, the altitudinal nature of the event, and the presence of vasculopathic risk factors.

The absence of the typical scintillation scotoma (e.g. positive visual phenomenon, jagged edge, colored lights, or fortification scotoma) or associated migraine headaches makes the diagnosis of migraine less likely even though this patient has a history for migraine.

Although GCA would be unlikely in a 44-year-old patient, I would consider the diagnosis in all cases of TVL in an older patient, and an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as other investigations for GCA might be warranted.

The bottom line in this case is that I am always hesitant to make a new diagnosis of "retinal migraine" in the absence of a classic history, multiple prior and stereotyped attacks without residual visual loss, and in an older patient. I am particularly concerned when the patient has other vasculopathic risk factors (older age, smoking, diabetes, hypertension, cardiac disease, or hypercoaguable state), and I typically defer to my colleagues in stroke neurology on the timing or need for admission for an inpatient evaluation. In patients with isolated TVL who have completely normal eye exams and who are not having repeated events, or in patients who have had multiple events without visual or neurologic sequelae over longer periods of time, I often concur with the outpatient ischemic work up. Patients with crescendo and recurrent events, a visible embolus, or transient hemispheric signs should probably be evaluated by a stroke neurologist on an urgent basis.

Dr. Brazis. Monocular TVL lasting 5 to 60 minutes (usually 2 to 30 minutes) is strongly suggestive of thromboembolic disease. Retinal emboli may arise from the aorta, carotid artery, or the heart. Patients often describe the TVL as a veil or shade descending or ascending over a portion of their visual field. Other patients complain of patchy visual loss ("Swiss cheese" pattern) or peripheral constriction with central visual sparing. Some episodes of monocular TVL are accompanied by a sensation of color or other photopsias. Episodes of monocular TVL due to thromboembolic disease rarely last several hours.

Patients with thromboembolic disease may demonstrate emboli within the retinal vessels. Emboli may be composed of clotted blood, fibrin, platelets, atheromatous tissue, white cells, calcium, infectious organisms (septic emboli), air, fat, tumor cells, amniotic fluid, or foreign materials (e.g. talc, artificial valve material, catheters, silicone, cornstarch, mercury, corticosteroids). The most common types of emboli seen in atherosclerotic disease of the aorta/carotid arteries or cardiac disease include the following:

- Cholesterol emboli (Hollenhorst plaques) are bright, glistening, yellow or copper-colored fragments, most often seen in peripheral arterioles in the temporal fundus. These emboli most often arise from atheromatous plaques in the aorta or carotid bifurcation.

- Platelet-fibrin emboli are dull, white, gray, often elongated, and subject to fragmentation and distal movement. These emboli most often lodge at bifurcations of retinal vessels and arise from the walls of atherosclerotic arteries or from the heart, especially from heart valves. They may also be seen in coagulopathies.
- Calcific emboli tend to be large, ovoid or rectangular, and chalky-white. These emboli often occur over or adjacent to the optic disc. They usually arise from cardiac (aortic or mitral) valves and less often from the aorta or carotid artery. Unlike cholesterol emboli, which often disappear in a few days, calcific emboli may remain permanently visible.

TVL may also occur from ocular hypoperfusion rather than embolization. In some patients, monocular TVL may occur when the patient is exposed to bright light. These patients usually have severe, ipsilateral carotid occlusive disease. Bilateral, simultaneous TVL induced by exposure to bright light may rarely occur with bilateral severe carotid stenosis or occlusion. The light-induced TVL probably reflects the inability of a borderline ocular circulation to sustain the increased retinal metabolic activity associated with light exposure. Alternating transient visual loss to bright light has also been described with GCA.

TVL may also occur with carotid artery dissection. In a review of the clinical features of 146 patients with extracranial carotid artery dissection, 41 patients (28%) had monocular TVL. The TVL was painful in 31 cases, associated with a Horner syndrome in 13 cases, and described as "scintillations" or "flashing lights" (often related to postural changes suggesting choroidal hypoperfusion) in 23 cases. Two of 23 patients with spontaneous carotid artery dissection experienced transient monocular blindness; in one of these patients, episodes were provoked by sitting up from a supine position.

Postprandial transient visual loss has also been described. It is proposed that postprandial visual loss may be a symptom of critical carotid stenosis, with retinal and choroidal hypoperfusion probably caused by a combination of mesenteric steal, decreased cardiac output, and abnormal vasomotor control.

TVL lasting 10 to 40 minutes may occur with central retinal vein occlusion or with an impending central retinal vein occlusion. Venous stasis retinopathy (i.e. hypotensive retinopathy), associated with severe carotid or ophthalmic artery occlusive disease, may also be associated with TVL. This syndrome is characterized by visual loss and ischemic retinal infarction, often accompanied by signs of ciliary artery obstruction, pallor of the disc, and hypotony. Venous stasis retinopathy may simulate Purtscher retinopathy (multifocal areas of ischemia) and be associated with a variety of fundus pictures:

- Minimal or no ophthalmoscopic changes in some patients with monocular TVL.
- Few widely scattered blot and dot hemorrhages and mild dilation of retinal veins (venous stasis retinopathy), usually in patients with minimal visual complaints.
- Dilation of the retinal arterial tree, dilation of the retinal veins, and cotton-wool patches.
- Retinal capillary changes, including microaneurysms, cystoid macular edema, and angiographic evidence of areas of capillary nonperfusion that may be confined to the areas along the horizontal raphe.
- Larger areas of peripheral capillary nonperfusion, retinal neovascularization, and hemorrhage.
- Any degree of branch retinal vein occlusion, branch retinal artery occlusion, and central retinal artery occlusion.
- Ischemic optic neuropathy.
- Fluorescein angiography showing diffuse retinal capillary telangiectasia, delayed retinal artery circulation time, late staining of the disc, and aggregations of microaneurysms around the pre-equatorial zone mimicking idiopathic juxtafoveal retinal telangiectasia.
- Any of the above associated with panuveitis, neovascular glaucoma, and a rapidly progressing cataract (ocular ischemic syndrome).

GCA may produce attacks of TVL lasting minutes to hours, indistinguishable from those produced by atheromatous disease. TVL probably results from intermittent inflammatory occlusion of the ophthalmic, posterior ciliary, or central retinal arteries. A postural form of TVL has been described in GCA

and a tenuous optic disc perfusion. Alternating monocular TVL may occur with GCA and may be induced by bright light.

TVL may also occur in association with antiphospholipid antibodies, hyperviscosity and hypercoaguable states, polycythemia vera, systemic lupus erythematosus, and hepatitis C associated type II cryoglobulinemia-mediated systemic vasculitis with mononeuritis multiplex. Arteriovenous malformations may divert blood flow from or reduce blood flow in the ophthalmic artery (ophthalmic steal syndrome). The TVL may alternate from eye to eye.

Vasospasm, especially associated with migraine, may also produce TVL without any of the visual phenomena typically seen during a migraine attack. Vasospasm of the retinal vessels has been documented by ophthalmoscopy during some attacks of monocular TVL. TVL, likely due to vasospasm and migraine, may be induced by exercise or sexual intercourse.

Intermittent angle closure glaucoma may also cause brief episodes of monocular TVL that are usually, but not always, associated with ipsilateral eye pain and occasionally simultaneous dilation of the pupil. Exercised-induced visual disturbances may also occur during attacks of pigmentary glaucoma. Episodes of monocular TVL lasting two to three minutes, induced by changes in posture, have been described following a scleral buckle procedure, likely due to intermittent obstruction of the central retinal artery blood flow by the encircling element. Finally, TVL may also be associated with congenital anomalies, peripapillary staphyloma, and morning glory syndrome. Episodes of TVL with these anomalies may last 15 to 20 seconds or up to 20 minutes, the latter mimicking TVL with thromboembolic disease. The episodes of TVL in peripapillary staphyloma may be associated with intermittent dilation of the retinal veins and may be orthostatic.

Patients with monocular TVL, lasting minutes, associated with visible retinal emboli, need to be evaluated for carotid and aortic vascular disease and cardiac valvular disease. Stroke risk factors (e.g. smoking, hypertension, diabetes mellitus, hyperlipidemia, etc.) should be evaluated and controlled. Studies to evaluate the carotid arteries include a carotid Doppler and ultrasound. Some

patients may require MR angiography and conventional angiography. Cardiac investigations include transthoracic and transesophageal echocardiography and cardiac MR imaging.

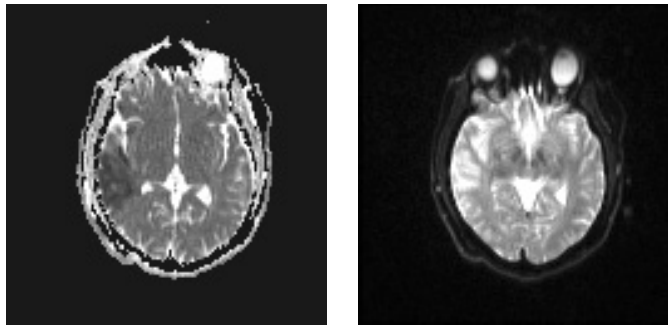
If no thromboembolic source for the episodes of TVL is documented, then further studies should be considered. These include MR imaging of the brain with MR angiography to investigate for possible brain ischemia, or less likely, a vascular malformation. Laboratory studies, including sedimentation rate, complete blood count, antiphospholipid antibodies, antinuclear antibodies, collagen vascular disease profile, and studies to investigate the presence of dysproteinemia.

Young patients (<45 years old) with monocular TVL are unlikely to have significant occlusive carotid disease (other than carotid dissection). A cardiac embolic source, as well as a vasculitis or coagulopathy, must be sought. As noted above, monocular TVL in younger patients has a more benign clinical course than that found in an older population, and migraine is a likely cause of many episodes. Calcium channel blockers (e.g. verapamil or nifedipine), if not otherwise contraindicated, may be considered in some of these patients to reduce the frequency of episodes of TVL.

Finally, all patients with monocular TVL lasting minutes should have a complete ophthalmoscopic examination to investigate for such conditions as intermittent angle closure glaucoma, morning glory syndrome, and peripapillary staphyloma. Spontaneous anterior chamber hemorrhage (hyphema) should also be considered, especially in patients with associated erythropsia and in those who have undergone cataract extraction.

Episodes of monocular TVL lasting hours are rare. However, such spells may occur with thromboembolic disease, as a postprandial phenomenon associated with critical carotid stenosis, and with migraine. Monocular TVL lasting hours may be a symptom of impending central retinal vein occlusion.

Course. The following day, however, she developed weakness of the left arm. She was seen in the Emergency Room (ER), and a CT scan and subsequent



(A) (B)

Fig. 14.1 (A, B) Diffusion restriction and ADI images show changes suspicious for a right frontoparietal infarct.

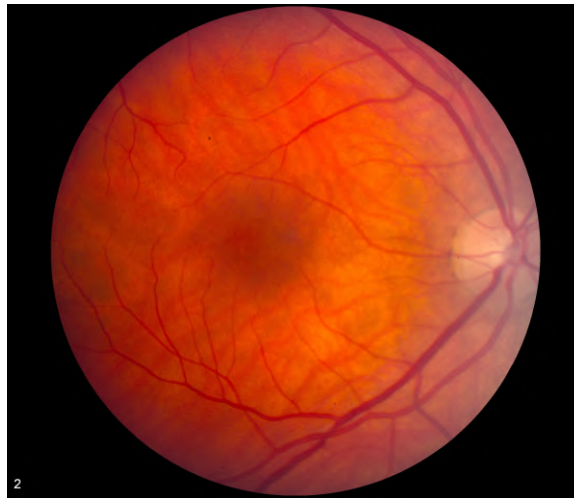


Fig. 14.2. Color photo of the right fundus.

cranial MR scan showed a right frontotemporal parietal infarct (Figs. 14.1A and 14.1B). An MRA showed a severe narrowing and hypoplastic right internal carotid artery A1 segment. The patient then had difficulty seeing objects and words to the left. Ocular examination showed a visual acuity of 20/20 OD and 20/20 OS. Fundus examination (Figs. 14.2 and 14.3) was normal. An MRA showed evidence of a right internal carotid artery dissection (Fig. 14.4).

Fig. 14.3. Color photo of the left fundus.

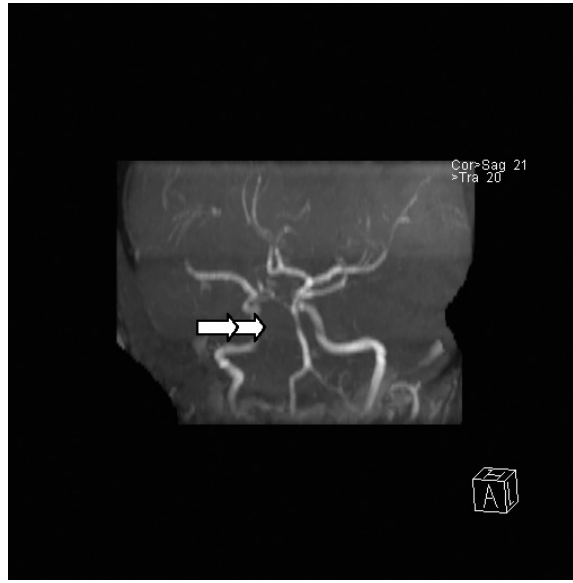


Fig. 14.4. MRA showing a severe narrowing and hypoplastic right internal carotid artery A1 segment suspicious for a carotid artery dissection.

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CHAPTER · 15

Jaw Pain and Headache in an Elderly Woman

CASE NO. 15

A 70-year-old woman presented with a three-week history of right-sided headache. She described the pain as dull and present throughout the day with no relieving factors. She also admitted to feeling unusually tired and had an unplanned 10 lb weight loss over the past one month. Over the previous few days, she described pain over the right jaw after chewing her food. She denied any visual symptoms. At a party the previous day, several friends commented on a prominent "bump" which had appeared on the right side of her head (Fig. 15.1). Her husband reported that she was reluctant to comb her hair due to the pain.

Her past medical history was significant for hypertension and osteoarthritis. Regular medication included metoprolol and ibuprofen. There was no family history of headaches. She was a non-smoker and did not consume alcohol.

On examination, her visual acuity was 20/25 OD and 20/30 OS. There was no relative afferent pupillary defect. Fundus examination showed possible mild disc pallor OU, and the Goldmann perimetry showed mild constriction. An OCT (optical coherence tomography) showed normal retinal nerve fiber layer OU. The remainder of the eye exam was normal.

Fig. 15.1. Prominent vessel on the right side of the head.

Discussion

Dr. Lee. Elderly patients who present with an acute onset of any of the following symptoms or signs should be considered as having giant cell arteritis (GCA) until proven otherwise:

- new onset headache
- jaw pain or fatigue with chewing
- neck or ear pain
- acute loss of vision
- transient visual loss
- bulging, tender temporal artery
- optic disc edema
- transient diplopia
- unexplained ophthalmoplegia.

Pain when combing the hair or tenderness along the temporal artery is highly suggestive of symptoms of temporal arteritis. A relatively normal eye exam should not dissuade the clinician from consideration of the diagnosis. The most common error for the ophthalmologist would be finding a normal eye exam and then either ignoring or misdiagnosing the headache and other constitutional symptoms. Patients with temporal arteritis may have a prior history of active symptoms of polymyalgia rheumatica (proximal muscle pain in the hip and shoulder girdle with morning stiffness). In patients suspected

of having temporal arteritis, I typically start empiric steroids and order both a serum erythrocyte sedimentation rate (ESR) and a C-reactive protein (CRP). Other acute phase reactants (e.g. elevated platelet count) could be considered, but I favor the ESR and CRP as screening tests, followed by a unilateral temporal artery biopsy. If the clinical suspicion is high for the diagnosis, I would proceed to a contralateral temporal artery biopsy if the initial biopsy was negative. I tend to treat with prednisone (1.0 to 1.5 mg per kg per day) during the evaluation phase. Although the evidence is somewhat controversial, I do consider intravenous steroids for patients who are monocular, have bilateral simultaneous or rapidly sequential visual symptoms or signs, have severe visual loss (especially if less than a few days of onset), or have transient visual loss. There is no prospective, randomized, head-to-head data comparing intravenous to oral steroids, however. Most of my patients with biopsy proven temporal arteritis require therapy for months to years. I write (or call) the primary care doctor to provide them with information about the diagnosis, warn them about the impending steroid-related side effects (especially in frail older patients), encourage them not to taper the steroids, and ask them to follow the patient and provide treatment for osteoporosis prophylaxis (e.g. vitamin D, calcium, DEXA bone density).

Dr. Brazis. I agree with Dr. Lee's comments. In our Clinic, we perform a temporal artery biopsy unilaterally and interpret this immediately via frozen section. If the unilateral biopsy is negative, we go on to perform a biopsy on the contralateral side. If the surgeon does not have the "luxury" of frozen section interpretation, I would suggest bilateral biopsies in most patients as the yield of doing the second side is perhaps 2 to 3%, and one never wants to miss this diagnosis because of the potentially catastrophic visual loss that may result if the diagnosis is missed and treatment is not continued. We also suggest intravenous corticosteroids in the scenarios described by Dr. Lee. We place all patients on aspirin, if there are no contraindications, as this agent may decrease subsequent ischemic risk; the evidence for the use of aspirin in GCA is anecdotal but might reduce the risk for future cardiovascular events or complications. Steroid sparing agents, including new monoclonal antibodies (e.g., tocilizumab), can help reduce the dose and duration of steroid treatment in GCA.

Course. Blood results were significant for an ESR of 16 mm/hr and a CRP 2.8 mg/dl (<1.5 normal). The patient was started on oral prednisone 100 mg per day. A temporal artery biopsy was performed despite the normal ESR and showed granulomatous arteritis on the biopsy. The patient was slowly tapered down on the prednisone over an 18-month duration and did not suffer any visual loss or other complications of therapy.

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CHAPTER · 16

Acute Bitemporal Hemianopsia

CASE NO. 16

A 56-year-old previously healthy man had been a passenger in a car driven by his son when he suddenly complained of headache, blurred vision, and dizziness. Shortly after this complaint, he lost consciousness, and his son drove him directly to the Emergency Room (ER). His level of consciousness improved, and he was brought to the Neuro-Ophthalmology Clinic for further evaluation. On examination, his visual acuity was 20/80 OD and 20/60 OS. There was no relative afferent pupillary defect. Fundus examination showed normal discs (Figs. 16.1 and 16.2). The initial consulting ophthalmologist had seen the patient and recommended that he be sent to the eye clinic when stable for a formal visual field. At the bedside, however, the neuro-ophthalmologist performed confrontation testing that suggested a bitemporal hemianopia. Three weeks later, a formal Humphrey visual field (Fig.16.3), however, confirmed the bitemporal hemianopsia.

Discussion

Dr. Lee. The acute onset of headache and a bitemporal hemianopia implicates a lesion at the level of the optic chiasm. The life-threatening etiologies for an acute chiasmal syndrome include suprasellar aneurysm and pituitary apoplexy. Chiasmal neuritis could produce the visual field defect and pain, but the loss of consciousness suggests a rapidly expanding lesion. Pituitary apoplexy is an

Fig. 16.1. Color picture of the right fundus.

Fig. 16.2. Color picture of the left fundus.

emergency because of the associated panhypopituitarism and potentially life-threatening cortisol deficiency, which might require emergent admission and hormone replacement. Surgical decompression might be urgently required as well for a rapidly expanding lesion producing other neurologic deficits (e.g. loss

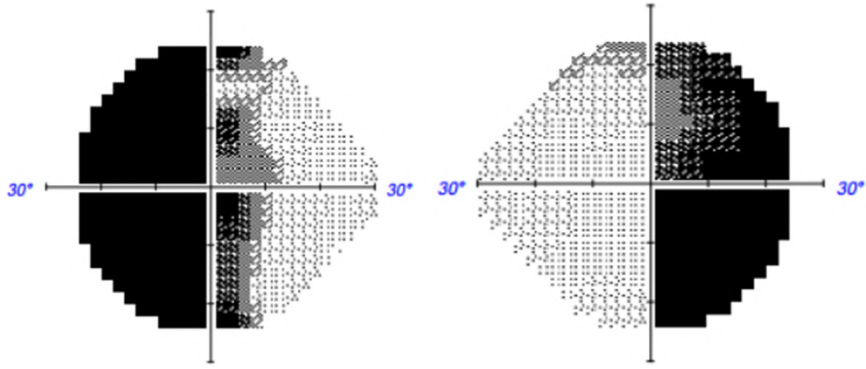

Fig. 16.3. Humphrey visual field showing a bitemporal hemianopia.

of consciousness as in this case). Although an MRI is generally superior to a CT scan for sellar lesions, a CT scan is faster to obtain and might show hemorrhage from apoplexy, which might allow earlier diagnosis and treatment for the patient. The important points for the ophthalmologist are that an acute painful bitemporal hemianopia should be imaged emergently even if the imaging is to be done after working hours or over the weekend and that patients with apoplexy need admission and evaluation for panhypopituitarism and other endocrine dysfunction. The key for the ophthalmologist seeing a patient at the bedside is to perform a confrontation visual field to confirm that the visual field defect is bitemporal and thus localizing. Waiting for the patient to have a formal perimetry out of convenience or delaying the diagnosis while waiting for the patient to be stable enough for transportation to the clinic is not recommended.

Dr Brazis. We warn all patients known to have a pituitary tumor about the possibility of pituitary apoplexy, i.e. sudden expansion of the tumor by ischemia or hemorrhage, and document this warning in the patient's chart. Patients with known pituitary tumors are instructed go to the ER immediately if they suffer any sudden, excruciating headache, sudden visual loss, or sudden diplopia. Emergency hormonal replacement and neurosurgical procedure may be lifesaving.

Course. Cranial CT and MRI scans showed a pituitary mass with hemorrhagic components (Figs. 16.4 to 16.8). His son reported in retrospect that the patient

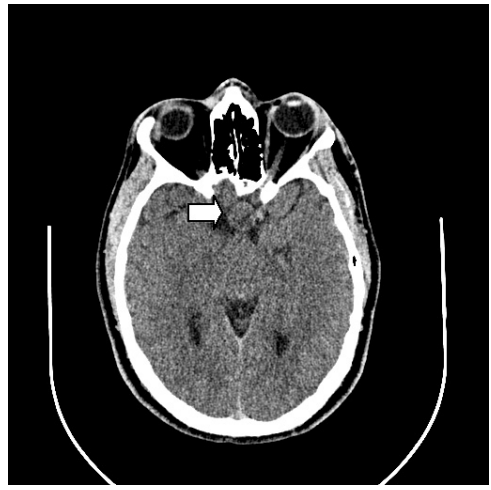

Fig. 16.4. Non-contrast CT head showing a mass labeled with an arrow.

Fig. 16.5. CT head showing areas of high density and low density within the mass.

had been seen in a follow-up for a benign "brain tumor" in the past, but the surgeons had told him that it did not need surgery yet, and his last cranial MRI scan performed two months ago showed no change. A CT scan in the ER showed a pituitary mass with areas of high density suspicious for a bleed (Figs. 16.4 and 16.5).

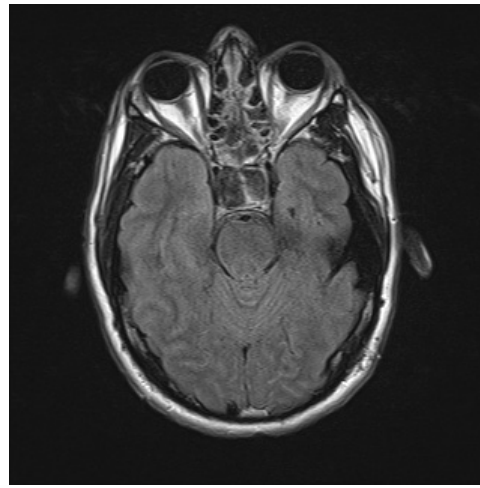

Fig. 16.6. Axial FLAIR MRI showing a large mass with areas of high and low signal within the sella consistent with a pituitary lesion.

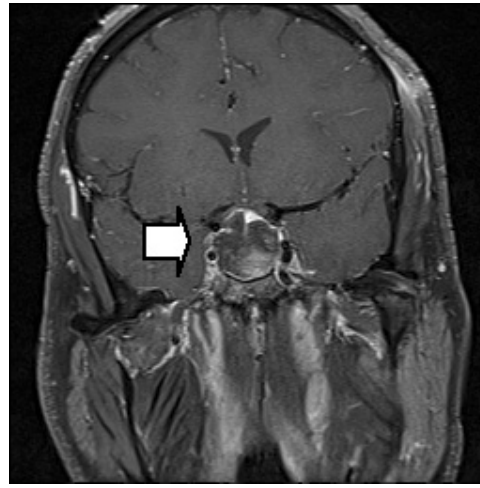

Fig. 16.7. Saggital MRI showing a large mass with rim enhancement and areas of high and low signal within suspicious for hemorrhage.

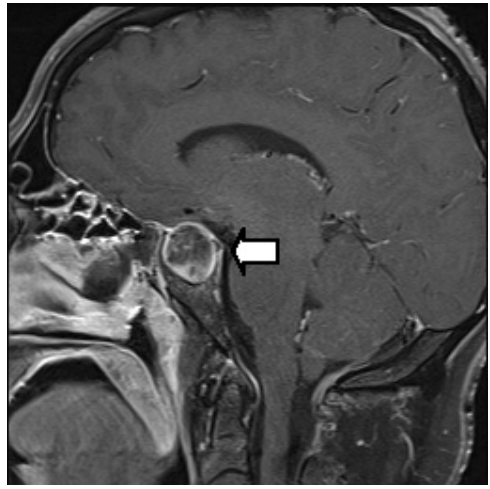

Fig. 16.8. Coronal MRI showing a large mass with rim enhancement and areas of high and low signal within suspicious for hemorrhage.

The patient underwent transsphenoidal decompression of his pituitary tumor with secondary apoplexy and recovered completely.

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CHAPTER · 17

Acute Anisocoria with Neck Pain

CASE NO. 17

A 54-year-old woman underwent chiropractic treatment for neck pain, and a few days after the neck manipulation, noticed her right lid started drooping. Her husband noticed that the right pupil was significantly smaller than the left. She denied any vision loss or diplopia. The patient reported worsening of her right-sided neck pain, and she was referred to the neuro-ophthalmology service. Past family history was significant for diabetes and hypertension. She did not smoke cigarettes or consume alcohol. She was allergic to penicillin and did not take any medication. The remainder of the medical history was non-contributory.

On examination, her visual acuity was 20/20 OU. The right pupil was miotic and measured 3 mm in the dark and 2 mm in the light with no afferent pupillary defect. The light and near reaction are normal in each pupil. The left pupil measured 4 mm in the dark and 2.5 mm in the light (Fig. 17.1). There was a 1 mm right ptosis and minimal "upside down ptosis" OD. A dilation lag was demonstrated OD clinically with the anisocoria greater at 5 seconds in dim ambient light as compared to 15 seconds. The remainder of the ocular and neurologic exam was normal.

Fig. 17.1. External photograph showing anisocoria with the right pupil smaller than the left in the light.

Discussion

Dr. Lee. The comprehensive ophthalmologist confronted with acute neck pain and anisocoria should first determine if the big pupil or the small pupil is the problem. The "big pupil" problem associated with pain is the pupil-involved third nerve palsy. The "small pupil" emergency is the Horner syndrome. Patients with a Horner syndrome may be harboring a lesion anywhere along the ocular sympathetic pathway from the hypothalamus, down the brainstem to the thoracic cord (C8-T2 level), up the sympathetic chain in the neck, to the internal carotid artery, the cavernous sinus, and finally the ipsilateral orbit. In the acute setting with pain, the major life-threatening etiology for a Horner syndrome is an ipsilateral internal carotid artery dissection. In this case, the right pupil is miotic, and the pupillary light and near reactions are otherwise normal in each eye. The anisocoria is greater in the dark than in the light. This implicates the small pupil as the abnormal pupil. In the setting of mild ptosis or upside down ptosis, this anisocoria is a Horner syndrome until proven otherwise. The dilation lag is confirmatory evidence for a Horner syndrome. The major differential diagnosis for the anisocoria would include physiologic anisocoria, but the constellation of findings in this patient suggests a Horner syndrome. In the

acute setting with convincing clinical findings, I would recommend performing a same day MRI study of the oculosympathetic pathway from the hypothalamus (i.e. cranial MRI) to the T2 level in the chest with particular attention to the ipsilateral internal carotid artery to exclude dissection. The history of chiropractic manipulation is suggestive of a potential mechanism for a carotid dissection. The evidence for the role of chiropractic manipulation is controversial, but anecdotal evidence suggests a possible causal relationship. Unfortunately, many patients are visiting the chiropractor because of neck pain, and perhaps these patients had pre-existing Horner syndrome that is coincidentally linked to the chiropractic manipulation and not necessarily causally linked. Topical cocaine has been the traditional pharmacologic test for distinguishing the Horner syndrome from physiologic anisocoria. Topical cocaine has become more and more difficult for comprehensive ophthalmologists to obtain and keep on hand in compliance with hospital, state, and federal regulatory policies and procedures. A topical cocaine test is generally considered positive if the post-drop anisocoria is 0.8 mm or greater. A follow-up hydroxyamphetamine test can localize the lesion to pre- or post-ganglionic location. Cocaine inhibits the re-uptake of norepinephrine at the junction, and a positive cocaine test confirms a Horner syndrome. In contrast, hydroxyamphetamine stimulates the release of norepinephrine at the junction and thus can distinguish a pre- from post-ganglionic Horner syndrome. Recently, we have been using topical apraclonidine for our Horner syndrome testing. Apraclonidine demonstrates a differential alpha-1 versus alpha-2 effects on normal and Horner syndrome pupils. In patients with a Horner syndrome, topical apraclonidine will reverse the anisocoria, with the larger pupil becoming smaller and the smaller pupil becoming larger (alpha-1 effect predominates from denervation supersensitivity). This endpoint is easier to detect and interpret than the post-drop anisocoria measurements for the topical cocaine test. In the acute setting, however, especially with neck pain, the clinician does not have time to perform these confirmatory and localizing pharmacologic tests, and it has been our practice to simply proceed to emergent imaging of the entire oculosympathetic pathway with a single MRI study of the head and neck with or without a concomitant MR angiogram (MRA) to exclude dissection. The distinctive radiographic sign of the carotid dissection is a crescent of high signal intensity on T1 that represents

the dissected segment and blood. Patients with an acute internal carotid artery dissection should probably be evaluated by the neurologist and considered for admission, further evaluation, and antiplatelet treatment. The role of anticoagulation (e.g. warfarin) versus antiplatelet treatment remains controversial, and this decision is best left to the admitting and treating neurologist. The main role of the ophthalmologist is to identify the Horner syndrome and order the appropriate neuroimaging study, including the neck. The most common error that the ophthalmologist can make in the evaluation of the Horner syndrome is imaging the head only and forgetting about the extracranial components of the oculosympathetic pathway. The major potential life-threatening etiologies for the Horner syndrome are the internal carotid dissection in the neck and a tumor in the lung apex (i.e. the Pancoast tumor), which would be missed if only the brain was imaged. The second most common neuroimaging error would be to order a computed tomography (CT) scan alone, as the MRI is more sensitive for the detection of the extracranial carotid dissection than the CT scan. The third most common diagnostic error is not realizing the urgency of evaluation for an acute Horner syndrome, as patients with an internal carotid dissection might suffer an ipsilateral hemispheric stroke from thromboembolic disease or have a potentially treatable dissection that requires emergent evaluation. The bottom line is that for this patient with an acute painful Horner syndrome after chiropractic manipulation of the neck, I would recommend an MRI and MRA of the head and neck to rule out extracranial internal carotid artery dissection. If apraclonidine or topical cocaine drops are available, it might be of interest to confirm the clinical suspicion, but if they are unavailable or if pharmacologic testing would delay the imaging, then I would just proceed to the neuroimaging study recommended above.

Dr. Brazis. A Horner syndrome may be caused by a lesion anywhere along the sympathetic pathway that supplies the head, eye, and neck. Associated symptoms and signs usually allow localization of the lesion.

When you see a patient with new anisocoria possibly related to a Horner syndrome, you should confirm the presence of a Horner syndrome pharmacologically (with cocaine or apraclonidine). The evaluation of an adult with Horner syndrome is mostly based on lesion location. The most classic cause of central (first-order

neuron) Horner is a lateral medullary infarction (Wallenberg syndrome); other causes include various thalamic, brainstem, and spinal cord lesions. Second-order Horner syndromes are most suggestive of neoplasm or trauma of the lower cervical spine, brachial plexus, or lung apex. Third-order Horner syndromes point to lesions of the internal carotid artery, such as dissection or cavernous sinus aneurysms. Further evaluation depends on the duration of symptoms, the presence of pain, other symptoms or signs, and the localization of the lesion to the first/second-order neuron or to the third-order neuron.

All patients need a physical examination (ocular, neurologic, neck, supraclavicular, and chest). The tests ordered would vary depending on the lesion location, the presence of associated symptoms or signs, the urgency of the work-up, and the radiologists' preference. If a first- or second-order Horner is present, we suggest a CT or MRI of the chest (to view pulmonary apex), MRI of head and neck with contrast, and possibly an MRA of the aortic arch or CTA (CT angiogram) of the head and neck. If a third-order Horner is present, we suggest MRI of the head with contrast and MRA or CTA of the head and neck. If localization of the Horner syndrome is unknown, we suggest imaging the brain, neck, spinal cord, carotid arteries, and pulmonary apex (may require multiple imaging tests). We feel that in this situation, the easiest test is MRI and MRA of the head, neck, and pulmonary apex using pre-defined Horner protocols. Some authorities suggest a CT/CTA of the head, neck, and chest, which allows good examination of the brain and spine, the soft tissues, and large blood vessels in the head, neck, and chest; it also allows examination of the pulmonary apex.

An acute painful Horner syndrome should be presumed related to a dissection of the ipsilateral internal carotid artery unless proven otherwise. These patients are at risk for cerebral infarction and should be evaluated emergently.

Course. External photographs were taken before (Fig. 17.2) and after pharmacologic testing. Note that the topical cocaine has eliminated the pre-drop test ptosis in the post-drop photos. Topical cocaine administration confirmed a right Horner syndrome (Figs. 17.3 to 17.4) with a residual

Fig. 17.2. External appearance prior to instillation of cocaine drops.

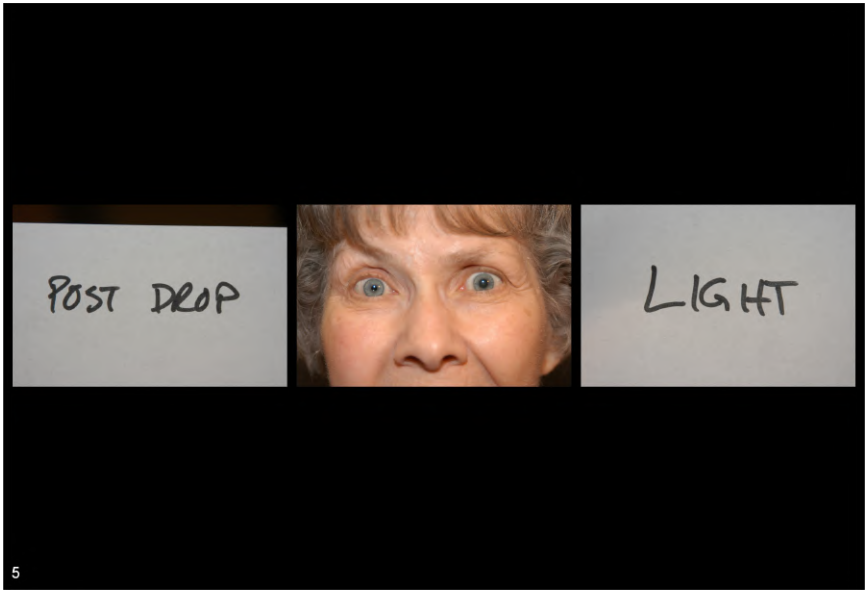

Fig. 17.3. External appearance following the administration of cocaine drops in the light.

Fig. 17.4. External appearance following cocaine administration in the dark.

Fig. 17.5. MRI with gadolinium contrast showing a right internal carotid artery dissection labeled with an arrow. The "crescent sign" of hyperintense T1 signal surrounding the dark circular flow void of the right internal carotid artery (black circle).

anisocoria of greater than 1 mm after the topical testing. An MRI scan of the neck showed a crescent sign of high intensity on the T1 surrounding the right internal carotid artery, consistent with a carotid dissection (Fig. 17.5). Following the MRI, the patient was admitted to the hospital and treated with antiplatelet therapy with aspirin. The brain MRI showed no intracranial ischemia. The neck MRA confirmed the right internal carotid dissection. Six months later, a repeat MRI and MRA of the neck showed the internal carotid dissection had healed completely. No further neurologic events had developed in the interim.

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CHAPTER · 18

Acute Painful Ophthalmoplegia

CASE NO. 18

A 37-year-old African American female presented with an acute onset of painful ophthalmoplegia OS. Her past medical, family, surgical, and social history were unremarkable. She was taking no medications. She did not smoke or consume alcohol. She had no other neurologic signs or symptoms.

Exam

The patient's visual acuity was 20/20 OU. The pupils were 4 mm OU and were reactive to light bilaterally. There was no relative afferent pupillary defect. The motility exam showed a primary position exotropia of 40 prism diopters that increased on gaze to the left to >55 prism diopters. There was limitation of adduction, elevation, and depression OD and there was a mild abduction deficit OD as well (Fig. 18.1). Her pain was limited to the V1 distribution on the face OD and she had mildly decreased cutaneous pinprick sensation in the V1 distribution on the right. The fourth nerve function seemed intact with intorsion in downgaze seen OD.

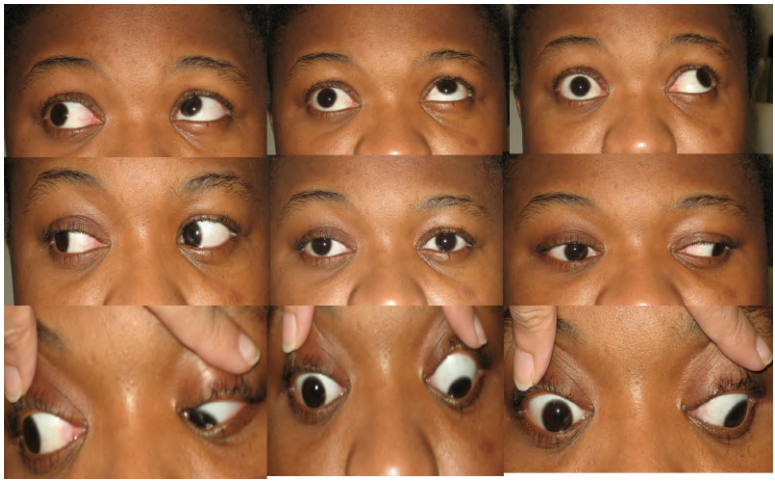

Fig. 18.1. Motility photographs show the limitation of elevation, depression, and adduction OD. There was a minimal abduction deficit OD as well with a small esotropia in the right gaze of 5 prism diopters. Note that the primary position deviation is not as large as one might expect from a medial rectus palsy alone, suggesting that the mild abduction deficit OD is an associated sixth nerve palsy.

Discussion

Dr. Brazis. In a patient with ophthalmoplegia and ophthalmic branch trigeminal (V1) distribution pain or numbness, a cavernous sinus lesion should be considered. The mild abduction deficit is also suggestive of a partial sixth nerve dysfunction. Combined ocular motor paresis and sympathetic denervation (not seen in this patient) are virtually pathognomonic of a cavernous sinus lesion. Compressive cavernous sinus lesions may also spare the pupil because they often preferentially involve only the superior division of the oculomotor nerve, which carries no pupillomotor fibers, or the superior aspect of the nerve anterior to the point where the pupillomotor fibers descend in their course near the inferior oblique muscle. The pupillary "sparing" with anterior cavernous sinus lesions may be more apparent than real, resulting from simultaneous injury of nerve fibers to both the pupillary sphincter and dilator, resulting in a mid-position, fixed pupil. The sympathetic fibers to the eye join the abducens nerve for a short distance within the cavernous sinus, and thus, a unilateral abducens nerve lesion associated with an ipsilateral Horner syndrome is of localizing value.

Pituitary adenomas, nasopharyngeal carcinomas, craniopharyngiomas, and metastases most commonly may cause a cavernous sinus syndrome. Sphenoid sinus carcinoma often causes a sphenocavernous syndrome but may also present with an isolated sixth nerve palsy (SNP). Nasopharyngeal carcinoma may compress the sixth nerve as many of these tumors arise from the fossa of Rosenmuller immediately beneath the foramen lacerum. Extension of the tumor through the foramen lacerum may cause a trigeminal sensory loss (e.g. affecting a V2 distribution) and an SNP. Thus, the combination of facial pain or V2 sensory loss with an SNP is a common presentation of nasopharyngeal carcinoma. Serous otitis media is a frequent accompaniment due to blockage of the Eustacian tube.

Carotid-cavernous sinus dural arteriovenous fistulae may present with unilateral or bilateral cavernous sinus syndromes. Tolosa–Hunt syndrome (THS), which is caused by inflammatory processes of various etiologies involving the cavernous sinus, presents with ocular motor weakness and retroorbital pain. Facial sensation and visual acuity may be diminished. THS or painful ophthalmoplegia is a diagnosis of exclusion. Sudden onset of headache and dysfunction of multiple ocular motor nerves on either one or both sides, with or without retroorbital pain or visual impairment, suggests the possibility of pituitary apoplexy. In all patients with a cavernous sinus syndrome, infectious etiologies, especially due to Aspergillus or Mucormycosis, are of concern, especially if the patient is immuno-compromised. The patient described needs neuroimaging (CT/MRI) with specific attention to the cavernous sinus and superior orbital fissure regions.

Dr. Lee. I completely agree with Dr. Brazis that the combination of an ispilateral third, fifth (V1), and in this case, a possible SNP suggests a cavernous sinus localization. The Tolosa–Hunt syndrome is a painful ophthalmoplegia syndrome that is typically steroid responsive and is as Dr. Brazis said, a "diagnosis of exclusion." I generally order an MRI with contrast and I direct specific attention to the ipsilateral cavernous sinus. The International Headache Society (IHS) redefined the prior diagnostic criteria for the entity known as the "Tolosa–Hunt syndrome" (THS). The diagnostic criteria require that granuloma be demonstrated by MRI or biopsy. La Mantia et al. reviewed the literature on THS from 1988 to 2002 and found 124 THS cases. Forty-four cases (35%)

had inflammation on MRI or biopsy, evidence of granuloma, and 41/124 (33%) had normal neuroimaging. Interestingly, 39 (31%) had a specific cause and so the THS was "secondary." The authors concluded that the clinical presentations for THS are common to several conditions and "their application alone does not guarantee a correct diagnosis."

Most of the cases of THS referred to me end up being secondary to an underlying and potentially treatable etiology, and I would recommend using the diagnosis of THS with caution.

Course. This patient underwent a contrast MRI (Fig. 18.2), which showed enhancement in the right cavernous sinus. An extensive evaluation for alternative etiologies was performed and was negative, and a presumptive diagnosis of the THS was made. Intravenous steroid therapy alleviated the patient's pain. In patients with a negative radiographic and laboratory

Fig. 18.2. Coronal MRI with contrast shows posterior cavernous sinus enhancement (arrow).

evaluation, complete resolution of clinical signs and symptoms and radiographic findings, and no recurrence of findings after steroid treatment, the diagnosis of THS can be presumed without necessarily pursuing a biopsy.

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Index

acute, 21–23, 49, 51, 91, 93, 96, 98, 101
acute pain, 1
amaurosis fugax, 127
anisocoria, 115–118, 147–150, 154
arterialization, 10, 11, 12

bartonella, 124, 125
bilateral, 33, 35, 39
bilateral ophthalmoplegia, 57, 60
bitemporal hemianopsia, 141

carotid-cavernous sinus fistula, 2
chronic ptosis, 9

diplopia, 4, 11, 49, 109, 110, 113
disc swelling, 105
dorsal midbrain, 57, 58

elderly woman, 137
emergency, 22
exophthalmos, 92, 95, 99
eye pain, 63

febrile patient, 41, 46
fever, 41, 42, 46

giant cell arteritis, 138

headache, 137, 138
homonymous hemianopsia, 15, 19, 21, 23, 41, 46
Horner, 116
Horner's syndrome, 148–151

ischemic, 51, 52

jaw pain, 137, 138

leukemia, 103–107

macular edema, 122, 124
mental status change, 57

monocular visual loss, 127
myelin oligodendrocyte associated disease, 73

neck pain, 147–149
neurological, 15, 16, 18
neurological sign, 115
neuromyelitis optica, 72, 73
neuroretinitis, 122, 124
nystagmus, 58, 59

ophthalmoplegia, 1, 2, 4, 5, 9, 12, 78, 79, 82, 84, 89, 109–111, 155, 156, 157
optic disc edema, 25, 26, 33, 35, 121–125
optic neuritis, 63, 66, 67
orbital, 92–101

painful, 21, 155, 157
painless, 15, 49
papilledema, 25, 27–29, 31, 35, 37, 39
pituitary lesion, 145
posterior communicating artery aneurysm, 87–89
posterior cortical artery, 22
proptosis, 10–13, 91–94, 96, 98–100
pseudotumor, 25–26
ptosis, 1, 2, 115–118, 147, 148, 151
pupil, 115–119
pupil involved, 85
pupil spared, 75

red eye, 1, 5, 91
retrochiasmal, 15, 16

sixth nerve palsy, 50
stroke, 16–20, 128, 129, 132
Subacute, 33

temporal arteritis, 138, 139
thalamus, 59
thiamine, 110–112
third nerve palsy, 75, 85, 86
Tolosa–Hunt syndrome, 157

visual field defect, 15, 16, 23, 41, 42, 141, 143
visual impairment, 27
visual loss, 64, 67, 71, 103–105
vomiting, 109–111

Wernicke, 110